Appendix 5: Paediatric HIV In The Western Cape

Prepared by Max Kroon and Brian Eley

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Glossary of terms and abbreviations

AZT	Zidovudine
BF	Breast feeding
PMTCT	Prevention of mother to child transmission
HIV	Human Immunodeficiency Virus
DNA	Deoxyribonucleic Acid
DOTS	Directly observed treatment support
NVP	Nevirapine
RNA	Ribonuvleic acid
PCR	Polymerase chain reaction
HAART	Highly active anti-retroviral therapy
AIDS	Aquired immunodeficiency syndrome
ARV	Anti-retroviral
RSA	Republic of South Africa
ANC	Antenatal Care
VCT	Voluntary counselling and testing
CCVT	Compulsory counselling and voluntary testing
CCT	Compulsory counselling and testing
FP	Family planning
STD	Sexually Transmitted disease
TOPS	Termination of pregnancy service
WHO	World Health Organisation
NGO	Non governmental organisation
LBW	Low Birth weight
UGA	Underweight for gestational age
IUGR	Intra-uterine growth restriction

NNRTI	Non-nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
Dual therapy intrapartum NVP	Combination of ZDV antenatally, and intrapartum + single dose
TB	Tuberculosis
ZDV	Zidovudine
IMR	Infant mortality rate
U5MR	Under 5 mortality rate

2. Introduction

As the Human Immunodeficiency Virus compromises host immunity, HIV infected children are more likely to acquire diseases caused by common childhood pathogens[1], tuberculosis and, as HIV disease progresses, opportunistic infections and end organ involvement. IF infected, these HIV positive children are more likely to have severe, life-threatening illness. This is particularly so where there is a high background infectious disease prevalence.

HIV/AIDS contributes significantly to worsening childhood health care indices in most of Sub Saharan Africa[2].

High rates of HIV infection, morbidity and mortality of care-givers further compromises the well being and survival of HIV exposed children and has much broader psychosocial and economic impact on the wider South African community into the future.

Table 1.2. HIV status of maternal deaths 2002-2004

	2002-2004	
HIV Status	**N**	**%**
Positive	1226	36.0
Negative	351	10.3
Unknown	1829	53.7

Paediatric HIV infection is almost always vertically acquired from mother to child. Without any intervention, the transmission rate may be as high as 25 - 48%[2] (antenatal 5 -10%; intra-partum 15% and post-natal up to a further 28% with prolonged *mixed breastfeeding*[3]). At all times the single most important determinant of transmission is a ***high viral load***.[4] Additional determinants are *mode of delivery* (avoidance of labour), *invasive obstetric procedures* and *prolonged rupture of membranes*. **Effective PMTCT interventions act at all these levels and have become the most important immediate determinants of vertical transmission.**

Prevention of mother to child transmission of HIV (PMTCT) has been shown to be almost 100% with maternal HAART and replacement feeding in the developed world.[5]

In **developing countries** where infectious diseases are common and resource constraints, infra-structural insufficiency and poverty are usual, HAART may not be

1 Mortality of infected and uninfected infants born to HIV-infected mothers in Africa: a pooled analysis.
Newell ML, Coovadia H, Cortina-Borja M, Rollins N, Gaillard P, Dabis F Lancet. 2004 Oct 2-8;364(9441):1236-43

2 Wiktor SZ, Ekpini E, Nduati RW. Prevention of mother-to-child transmis-
sion of HIV-1 in Africa. AIDS 1997;11(suppl B):S79-87.

3 Coutsoudis A, Pillay K, Spooner E, et al. Influence of infant-feeding patterns on early mother-to-child transmission of HIV-1 in Durban, South Africa: a prospective cohort study. South African Vitamin A Study Group. Lancet. 1999;354:471–476.

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deliverable to pregnant women. Replacement feeding (or lack of breastfeeding) may be associated with an increase in morbidity and mortality from malnutrition and infections.[6] However, results from clinical trials of fairly **simple PMTCT protocols** in these settings have shown that **a reduction in HIV transmission to as little as 2% is possible.**[7]

Early diagnosis is critical to facilitate comprehensive care of infected children, evaluate the effectiveness of PMTCT programmes, allay parental concerns and stratify health care services. [8, 9]

The care of HIV-infected children is constrained by many factors. The major paediatric treatment challenges are: (1) the size of the paediatric HIV burden relative to the available resources to address the care needs of these children,.(2) inadequacy of care before HIV-infected children require antiretroviral therapy and (3) the delivery of antiretroviral therapy to HIV-infected children and the quality of care they receive.

These challenges operate in all nine provinces including the Western Cape, and are influenced by many immediate and upstream determinants including the effectiveness of PMTCT and programs to modify the extent of the heterosexual epidemic

In this section, the immediate and upstream factors that compromise the success of the PMTCT and paediatric HIV management programs will be explored. Factors that compromise the health outcomes of HIV exposed children (infected and uninfected) will be discussed. Evidence will be led for immediate, underlying and basic level interventions which improve the efficacy of the PMTCT and Paediatric HIV management programs.

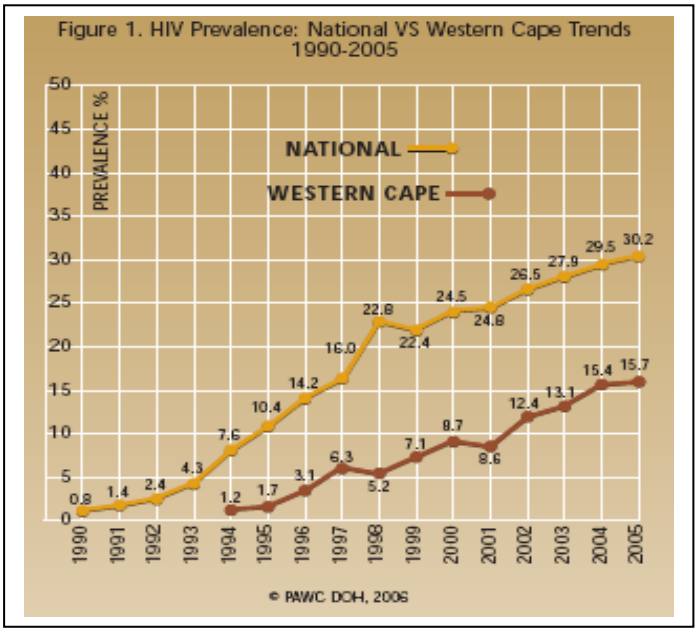
6 WHO Collaborative Study Team on the Role of Breastfeeding on the Prevention of Infant Mortality. Effect of breastfeeding on infant and child mortality due to infectious diseases in less developed countries: pooled analysis. Lancet 2000 Feb 5;355(9202):451-5.

7 Lallemant et al. Single-Dose Nevirapine plus Standard Zidovudine to Prevent Mother-to-Child Transmission of HIV-1 in Thailand. N Engl J Med July 2004; 351;3:217-228

8 Stevens W, Sherman G, Cotton M, Gerntholtz L, Webber L. Revised guidelines for diagnosis of perinatal HIV-1 infection in South Africa. Southern African Journal of HIV Medicine 2006;Issue22:8-14

9 World Health Organization. Antiretroviral therapy of HIV infection in infants and children in resource-limited settings: towards universal access. Recommendations for a public health approach, 2006. URL: http://www.who.int (accessed 19 August 2006).

3. **Prevalence**



In South Africa there are an estimated 5,54 million people who are infected with HIV[5].

The Western Cape is relatively privileged to be the province with the lowest HIV prevalence rate in RSA (15,7%) but this rate is rising steadily (Figure 1.)[1]
It is also the province with the second fastest growing population in South Africa.[2]
These new arrivals originate in the Eastern Cape (lowest rate of population growth) – an area of high HIV prevalence, child mortality and socio-economic deprivation.

TABLE 1. HIV Prevalence for the Western Cape by Area 2003-2005

DISTRICT	AREA	HIV PREVALENCE (95% CI)		
		2003	2004	2005
Cape Metropole	Blaauwberg	4.4 ± 3.0	1.2 ± 1.0	7.3 ± 3.6
	CapeTown Central	11.6 ± 5.0*	13.7 ± 4.7	11.5 ± 3.3
	Greater Athlone	10.1 ± 4.4	16.4 ± 3.6	17.7 ± 3.5
	Helderberg	19.1 ± 4.2	18.8 ± 3.3	12.6 ± 3.0
	Khayelitsha	27.2 ± 4.2	33.0 ± 3.5	32.5 ± 3.2
	Mitchells Plain	6.3 ± 4.0	12.9 ± 3.0	5.1 ± 2.0
	Gugulethu/Nyanga	28.1 ± 4.2	29.1 ± 2.8	29.1 ± 3.9
	Oostenberg	16.1 ± 4.3	14.8 ± 3.3	16.2 ± 3.5
	South Peninsula	9.3 ± 3.6	10.8 ± 3.2	12.4 ± 3.2
	Tygerberg Eastern	7.9 ± 3.9	12.7 ± 3.6	15.2 ± 3.5
	Tygerberg Western	8.1 ± 3.3	15.1 ± 4.0	15.0 ± 3.1
Overberg	Bredasdorp/Swellendam	1.1 ± 2.1	10.0 ± 5.0*	4.5 ± 3.2
	Caledon/Hermanus	14.2 ± 4.6	12.5 ± 3.2	15.4 ± 3.2
Cape Winelands	Ceres/Tulbagh	7.5 ± 5.1*	10.5 ± 3.7	13.8 ± 4.6
	Worcester/Robertson	3.9 ± 2.6	8.4 ± 3.3	8.1 ± 2.4
	Paarl	10.1 ± 3.9	8.9 ± 3.0	11.4 ± 3.2
	Stellenbosch	8.5 ± 4.9	17.8 ± 6.1*	15.5 ± 4.8
West Coast	Malmesbury	10.7 ± 4.6	6.2 ± 3.7	7.6 ± 3.2
	Vredenburg	10.0 ± 4.5	13.0 ± 4.1	6.9 ± 3.5
	Vredendal	3.9 ± 3.4	5.8 ± 4.0	9.9 ± 4.0
Eden	Knysna/Plettenberg Bay	15.6 ± 4.0	17.4 ± 3.6	21.1 ± 4.5
	Klein Karoo	5.4 ± 3.2	6.5 ± 4.4	5.3 ± 3.0
	Mossel Bay/Hessequa	13.3 ± 4.6	12.5 ± 3.2	8.9 ± 4.5
	George	11.6 ± 3.7	13.3 ± 3.4	13.6 ± 3.5
Central Karoo	Central Karoo	6.5 ± 4.4	8.9 ± 4.6	8.9 ± 5.5

There are also certain health districts with very high prevalence (Table1)[10].
Most notable of these are Khayelitsha, Nyanga and Knysna/Plettenberg Bay.
There are also sub-districts (e.g. Masiphumelele)[3] with very high prevalence which are not reflected in the district statistics and need to be clearly identified

[1] Department of Health, Western Cape. Results of the HIV Antenatal Provincial and Area Surveys 2005.
[2] National Census 2001
[3]

The national antenatal sero-prevalence survey in 2005 shows that nationally 30,2% (Western Cape 15,7%) of pregnant women are HIV positive at booking[1]. Without any intervention, 20 – 48% will transmit HIV to their babies.

In the Cape Metropole alone, there are 70000 babies born each year.[2] Without intervention, this would translate into 5000 new cases of Paediatric HIV per annum. Without ARV's, most HIV infected children will become sick, hospitalised and die (after significant consumption of health care resources). If the PMTCT program reduces mother-to-child transmission rates to 2%, only 220 babies will become infected. The numbers speak to a highly cost effective intervention.[3]

Current overall Western Cape transmission rate (patients receiving PMTCT) is 6,1% but is apparently only 3% in Khayelitsha which is the district with the longest running PMTCT program[4]. This may however be an under estimate of the true rate of transmission as up to 20% of infants default follow up and it is likely that some children with early rapidly progressive HIV/AIDS may not survive to testing at 14 weeks of age. In addition, it is clear from a survey at Red Cross Childrens' Hospital that up to 28,9% of the mothers of HIV infected patients on the general wards were not tested antenatally[5]. It is clear therefore that there are problems implementing PMTCT or the patients are coming from outside this province.

Transmission rates were about 2% in the "Thai" Trial on which our ARV regimen is based. The higher rate of transmission in the Western Cape program (which has added targeted HAART) might be explained by postnatal transmission from mixed feeding or suboptimal PMTCT due to late initiation of ARV's.

At present there are 230 000 – 300 000 HIV-infected children less than 15 years of age countrywide[6], of these 10 000 – 12 000 live in the Western Cape[7]. This translates to an absolute prevalence rate of approximately 3%. At least 50% of these children should be on anti-retroviral therapy. However, based on a telephonic survey of the nine provincial HIV/AIDS Directorates, at the end of March 2006 it was estimated that less than 15 000 children were receiving therapy nationally.[8] [9] At present more than 2900 children are receiving HAART in the Western Cape.[10]

1 Department of Health. National HIV and syphilis antenatal seroprevalence survey in South Africa 2005.

2 Van Heerden, Nongena: PMNS PPIP data. 2006

3 Marie-Louise Newell, Francois Dabis, Keith Tolley and David Whynes: Cost-effectiveness and cost–benefit in the prevention of mother-to-child transmission of HIV in developing countries for the Ghent International Working Group on Mother-to-Child Transmission of HIV. AIDS 1998, 12:1571–1580

4 Pieters, Pauline. : Personal Communication. HIV directorate, Dept of Health, PGWC

5 Eley,B. Personal communication

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8 Eley, B. Personal Communication 2007

9 Meyers T, Moultrie H, Naidoo K, Cotton M, Eley B, Sherman G. Challenges to Paediatric Care and Treatment. J Infect Dis 2007 (in press)

10 HIV/AIDS Directorate, Western Cape Department of Health. Western Cape Antiretroviral Treatment Programme monthly report, January 2007

4. HIV and childhood morbidity and mortality

Paediatric HIV infection was implicated in at least ***50% of under 5 in-patient mortality*** in South Africa in 2000[11] with young infants particularly at risk. While significant progress has been made in the Western Cape, ill HIV infected children continue to contribute significantly to inpatient workload (30-50%), bed occupancy and outpatient work[12]. This in turn ***impacts on the care of non-HIV infected patients*** due to the non-availability of appropriate hospital beds and staff (postponed surgery and patients in inappropriate level of care beds).

HIV infection is intimately linked to the major causes of childhood morbidity and mortality[13] (i.e. pneumonia, diarrhoea, malnutrition, low birth weight and sepsis) and is most probably the reason why pneumonia[14] has overtaken diarrhoeal disease as the leading cause of childhood death.

Studies in South Africa and other developing countries have consistently shown high mortality and morbidity rates in HIV exposed children with HIV infection increasing mortality risk 6 fold.[15]

Data on morbidity and mortality rates for HIV-infected and HIV-free children on the Western Cape PMTCT program are not readily available. There are suggestions that these rates may be high in the impoverished areas in which HIV infection is common – particularly with formula feeding in environments where frequent infections contribute significantly to the background childhood mortality rate.

TABLE 11: The infant mortality rate and under-five mortality rate in South Africa in 2000

Province	Infant mortality rate Deaths per 1,000 live births	Under-five mortality rate Deaths per 1,000 live births
Eastern Cape	71.0	105.0
Free State	62.0	99.0
Gauteng	44.0	74.6
KwaZulu-Natal	68.0	116.4
Limpopo	52.0	80.7
Mpumalanga	59.0	99.8
Northern Cape	46.0	68.1
North West	55.0	88.5
Western Cape	32.0	46.3
South Africa	**59.0**	**95.0**

Source: Bradshaw D, Nannan N, Laubscher R, Groenewald P, Joubert J, Nojilana B, Norman R, Pieterse D & Schneider M (2004) *South African National Burden of Disease Study 2000 – Estimates of Provincial Mortality*. Cape Town: South African Medical Research Council, Burden of Disease Unit.

While the average child mortality rate in the Western Cape is below the national average, there are health districts where it is significantly higher. In Cape Town, these district are Nyanga and Khayelitsha which have the highest rates of recently arrived migrants from the Eastern Cape and large crowded informal settlements where infrastructure is lacking and there is significant overcrowding. These coincide with areas of high antenatal HIV seroprevalence and it may therefore imply that HIV is a

11 Bradshaw D, Bourne D, Nannan N. MRC Policy Brief No3, 2003

12 Eley, B. Personal Communication 2007

13 Obimbo EM, Bori-Ngacha DA, Ochieng JO, Richardson BA, Otieno PA, Bosire R, et al. Predictors of early mortality in a cohort of human immunodeficiency virus type 1-infected African children. Pediatr Infect Dis J 2004;23(6):536-43.

14 Angelika Krug, Mark Patrick, Robert C. Pattinson & Cindy Stephen. Childhood death auditing to improve paediatric care. Acta Pædiatrica, 2006; 95: 1467_1473

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major association – this is borne out by the causes of death in hospitals receiving sick children from these areas[16].

Furthermore it is even more difficult to measure "collateral" morbidity and mortality due to "spill-over" reduction in breast-feeding in the non-HIV exposed population as a result of officially sanctioned replacement feeding policies.

5. Impact beyond childhood morbidity and mortality

High rates of HIV infection, morbidity and mortality of care-givers further compromises the well being and survival of HIV exposed children[17] and has much wider psychosocial and economic impact on the broader South African community into the future. Orphans, homelessness and adolescent psychopathology with roots in infant attachment problems[18] These social, psychological, cultural, economic, political and spiritual ramifications are hopefully addressed by the Infectious Disease and Mental Health Groups.

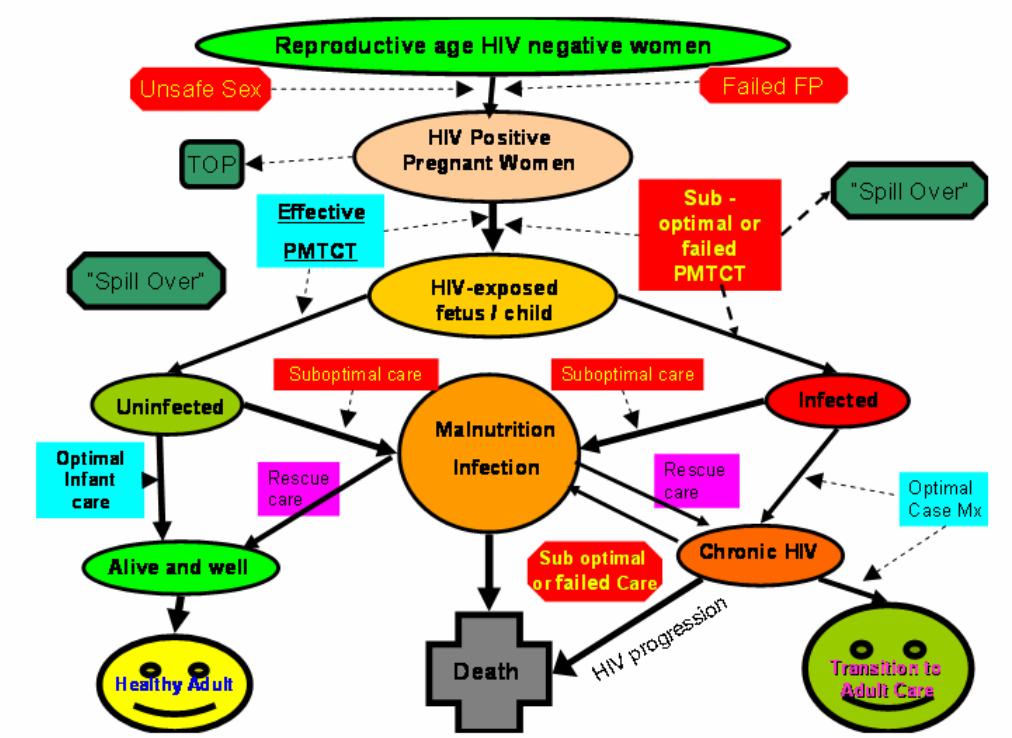
[16] Eley,B. Personal communication, 2007

[17]

[18]

Fig 2**:** Conceptual framework: *Prevention* ***by safe sex, effective family planning and PMTCT***, ***early*** *case detection* **and** ***optimal*** *case management* **are key Health Care interventions for the** ***best*** *health outcome* **for vertical HIV exposure.**

6. Determinants of poor health outcome in vertical HIV exposure



In addition, ***optimal infant care*** is essential to *minimise postnatal HIV transmission* while *optimising the nutritional status and immune defences* of HIV exposed infants (HIV infected and uninfected) to reduce morbidity and mortality associated with replacement feeding and common childhood infectious diseases. Feeding policy should recognise and actively counteract the dangers of a *"spill over effect"* of formula feeding on the *majority* population of infants not exposed to HIV.

Suboptimal care results in HIV progression, malnutrition and life threatening infectious diseases, which require expensive and resource consuming ***rescue care.***

Rescue Care is the ***expensive*** set of interventions needed to salvage children who have been compromised by sub-optimal care or HIV disease progression despite HAART.

7. PMTCT

General

As almost all paediatric HIV is vertically transmitted, the PMTCT program is the **critical rate-limiting intervention at the gateway to the paediatric HIV epidemic**. It is crucial to the success of the paediatric component of Government's Comprehensive HIV and AIDS Care Strategy[1].

Prevention of new paediatric HIV infection should remain a priority. It should not be neglected while attention and resources shift to the roll out of ARV therapy to HIV infected adults and children.

However there is a potential "down side " to this intervention – scarce resources may be diverted from other aspects of child health care and the replacement feeding component of PMTCT in particular may undermine the health benefits of exclusive breast feeding in the general population.

While primary prevention of vertically transmitted HIV is very important, HIV ***transmission rate is not the only measure of the effectiveness*** of a PMTCT program. Health outcomes need to be measured in terms of mortality, morbidity and impact on child health in general as well.

An important additional health outcome is "collateral" mortality and morbidity due to unsafe feeding practices, sub-optimal immunity of HIV free infants of HIV positive mothers and perhaps hazardous environments (increased opportunistic pathogens) including ill or absent caregivers/breadwinners. HIV-free survival (HFS) and morbidity in HIV exposed infants are not routinely measured as part of PMTCT programs and indeed it is difficult to do so.

The PMTCT program is sub-optimal if:

1. Rate of *transmission is high*.
2. *Morbidity and mortality* of HIV exposed children (PCR positive and negative) is high.
3. Program *impacts negatively on child health* in general ("spill-over").
4. Program *impacts negatively on family health* and well being (orphans, transport costs, hidden formula milk costs, etc).
5. Program *impacts negatively on other aspects of the Health Service* (e.g. BFHI and community based exclusive breast feeding support programs).

The key immediate determinants of a suboptimal PMTCT intervention are:

1. Under-utilisation of Family Planning Services and late ANC or non-booking by HIV positive women
2. Poor uptake of HIV testing
3. Sub-optimal choice of ARV regimen
4. Late infant PCR testing
5. Unsafe infant feeding policy
6. Maternal death

[1] Dept of Health, RSA: Comprehensive HIV and AIDS Care Strategy. 2006

Poor control of the heterosexual epidemic is a **fundamental underlying determinant** of PMTCT failure and is investigated by the **Infectious Diseases Task Group**.

Suboptimal data capture compromises analysis of the program's success and comparison to expected rates of transmission. Monitoring of mortality, morbidity and child health indicators in addition to MTCT rates are crucial to monitoring the program's impact.

The above key immediate determinants are influenced by underlying **caregiver** factors such as poor maternal and bread-winner health, level of education, maternal financial dependence, lack of disclosure and poor family support.

Underlying **household** factors include housing that is often informal and temporary in crowded peri-urban settlements with poor sanitation, distant unsafe water and energy dependent on the burning of solid fuel or paraffin. Other household factors such as unemployment, access to transport, food insecurity and land tenure problems, further underpin the determinants of PMTCT failure.

Local and provincial government capacity limitations and corruption further compromise service, transport infrastructure, social grants and housing delivery.

In the **community** gender inequality, fear of stigmatisation and discrimination all conspire to compromise PMTCT delivery further particularly as confidentiality requirements result in encrypted documentation of HIV status causing health care worker confusion and lost opportunities for intervention particularly when patients are referred across levels of care[2]**.** A mobile population of recently arrived employment seeking migrants, lack of a seamless PMTCT program interface with the Eastern Cape and constant population movement between the provinces results in population instability which compromises program continuity and delivery from early pregnancy to maternal and paediatric follow up care.

At a more **basic level** these factors have their roots in the legacy from the previous government's policy of forced removals and separate development.[3]

Health care system factors like limited capacity, logistics and infrastructure deficiencies, crowded facilities, resource and budget constraints, are likely to beimportant underlying determinants of poor PMTCT service implementation.

Beyond these underlying factors are the **basic determinants** of ineffective PMTCT which include poverty, unfavourable macro-economic policy and a political leadership who lack consistent political will and at times subscribe to denialist dissident ideology thus undermining the efforts of health care workers and people living with HIV to address this scourge.

The Western Cape PMTCT Program revision has been delayed by sluggish and inadequate National HIV/AIDS Policy Framework development and centralised

2 Kroon SM. Personal observation, 2006.

3 Msokoli Qotole Early African Urbanisation in Cape Town: Windermere in the 1940s and 1950s African Studies, 60, 1, 2001

control by means of threats of budget limitation resulting in delays in prioritising critical human resource development.

1. Under-utilisation of Family Planning Services and late ANC or non-booking by HIV positive women

Prevention of new HIV infection in reproductive age women and prevention of unwanted pregnancy in HIV positive women[4] (including access to Termination of Pregnancy Services) need to be adequately addressed or the opportunity to reduce the number of pregnant HIV positive women will be lost.

The former should be covered by the Infectious Diseases Group but unfortunately there is no Sexual and Reproductive Health Group to deal with the latter.

HIV sero-conversion during pregnancy and lactation is associated with high rates of antenatal and postnatal MTCT and is a result of unsafe sexual activity[5].

Underlying determinants of poor uptake of Family Planning Services by HIV positive women include cultural issues, denial, infrastructure inadequacy, access and gender inequality.

Underpinning these factors are basic determinants such as poverty, economic dependence and lack of education.

Late pregnancy determination, non-booking and high rates of fetal growth restriction[6] result in under-estimates of gestational age, late commencement of ARV's and birth before adequate HAART.

Immediate determinants of late ANC booking include a long standing culture of only booking when the pregnancy is visible (most probably a result of historically limited health system capacity and high patient numbers), poor access (including limited crowded antenatal facilities far from patient's homes) and no reliable, affordable transport link. Substance abuse has also been shown to be associated with failure to access antenatal care.[7]

Beyond the factors underlying inadequate antenatal care are more basic determinants such as poverty, unemployment, migration from the Eastern Cape[8] and lack of education as to the benefits of early antenatal care.

4 Reynolds HW, Janowitz B, Homan R, Johnson L. The Value of Contraception to Prevent Perinatal HIV Transmission. Sexually Transmitted Diseases June 2006;0633(6):350-6.

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6 Saving Babies 2003, MRC…

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8 Human, Kroon, Bergman, Fawcus, Mtwana; Patient population movement in a Cape Town obstetric service. SAMJ Sept 2003, Vol 93, No. 9

2. Poor uptake of HIV testing

Early identification of HIV positive pregnant women is a key determinant of successful PMTCT program implementation.

A common reason for non-testing is failure to access antenatal care and this is dealt with in 1. above.

Testing may be refused for a number of immediate reasons including feelings of disempowerment ("HIV is incurable"), fear of bad news, fear of stigmatisation and discrimination (workplace and community), denial and fear of domestic consequences (loss of domicile, relationship and income).

Early in the Western Cape PMTCT program, voluntary counselling and testing (VCT) resulted in low acceptance rates.

Testing is currently not done during labour resulting in another missed opportunity to implement proven peri-natal PMTCT interventions in women of unknown HIV status at this specific time[9].

Delay in testing women of unknown status immediately after delivery increase the risk of HIV transmission because of mixed feeding and delays in ARV administration to the neonate.

Both of the preceding points are because of a need to respect individual rights to informed consent and adequate counselling in line with WHO recommendations.

Staffing and privacy constraints further compromise capacity to deliver counselling and testing services at these times. Open plan post natal and labour wards are not conducive to confidential counselling and dedicated counselling rooms are in short supply. High patient load and limited capacity at MOU's for booking (Staff and space shortages) and counselling (space, numbers of counsellors) compromise testing further.

3. Sub-optimal ARV regimens

Sub-optimal PMTCT ARV regimens result *in* ***unnecessarily high HIV transmission*** rates with consequent high child morbidity and mortality.

Toxicity and drug resistant virus are additional consequences of these regimens.

PMTCT ARV's may act *antenatally, during labour and delivery or in the post partum* period. They work by reducing viral load in pregnancy and in labour and by trans-placental foetal "ARV pre loading".

9 Forsyth BW, Barringer SR, Walls TA, Landry ML, Ferguson D, Tinghitella TJ, Unfricht M, Luchansky E and Magriples U. Rapid HIV testing of women in labor: too long a delay. J Acquir Immune Defic Syndr 2004; 35 (2): 151-4.

ARV regimens in common use:

Prevention of mother to child transmission of HIV has been shown to be almost 100% with maternal HAART, elective Caesarean section, neonatal Zidovudine and replacement feeding in resource rich settings,.[10]

The modified dual therapy "Thai" protocol has been shown to reduce transmission rates to close to 2% in a developing country setting (Thailand)[7]. Dual PMTCT therapy (especially maternal NVP component) may lead to NNRTI resistance with implications for subsequent ARV therapy.[11]

Simple modified oral Zidovudine monotherapy regimens reduce HIV transmission by approximately 50%with much less potential for virus drug resistance[12].

While NVP mono-therapy regimens targeting transmission during labour are better than nothing, they only reduce transmission by 47%[13] and induce high rates of virus drug resistance compromising subsequent HAART. This resistance may however be temporary.

There is some evidence suggesting that even in the absence of maternal ARV's, **neonatal** mono- or dual therapy prophylaxis within 72 hours of delivery may reduce transmission by a similar amount.[14]

The **immediate determinants** of sub-optimal ARV regimens are:

- If an HIV test was not done prior to pregnancy or during ANC (see 1. and 2 above) and **HIV status is unknown** during labour, at delivery or in the early neonatal period, patients will not normally have access to PMTCT.
- **high viral load** is associated with advanced maternal HIV disease or antenatal sero-conversion. Patients with high viral loads on simple cheap ARV regimens, common in developing countries, are more likely to transmit HIV to their offspring during pregnancy, labour, delivery and infancy. Less active ARV regimens targeting perinatal transmission only, may not be sufficient to prevent MTCT in patients with high viral loads at risk of antenatal transmission.

10 Thorne, Claire; Newell, Marie-Louise. Prevention of mother-to-child transmission of HIV infection. Current Opinion in Infectious Diseases. 17(3):247-252, June 2004.

11 N Martinson, L Morris, G Gray, D Moodley, P. HIV resistance and transmission following single-dose nevirapine in a PMTCT cohort - 11th Conference on Retroviruses and Opportunistic Infections, 2004

12 5 Lallemant M, Jourdain G, Le Coeur S, Kim S, Koetsawang S, Comeau AM, et al. A trial of shortened zidovudine regimens to prevent mother-to-child transmission of human immunodeficiency virus type 1. Perinatal HIV Prevention Trial (Thailand) Investigators. N Engl J Med 2000;343:982-91.

13 Guay LA, Musoke P, Fleming T, Bagenda D, Allen M, Nakabiito C, Sherman J, Bakaki P, Ducar C, Deseyve M, Emel L, Mirochnick M, Fowler MG, Mofenson L, Miotti P, Dransfield K, Bray D, Mmiro F, Jackson JB. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial. Lancet. 1999 Sep 4;354(9181):795-802

14 Taha E Taha, Newton I Kumwenda, Amanda Gibbons, Robin L Broadhead, Susan Fiscus, Valentino Lema, George Liomba, Chiwawa Nkhoma, Paolo G Miotti, Donald R Hoover. Short postexposure prophylaxis in newborn babies to reduce mother-to-child transmission of HIV-1: NVAZ randomised clinical trial. Lancet 2003; 362: 1171–77

- Specific drug factors such as pharmacodynamics, pharmacokinetics, need for refrigeration and formulation may affect **efficacy**. Poor compliance, sub-optimal ANC, late testing and shortened antenatal ARV **duration** are all associated with reduced efficacy. ARV regimens with **low efficacy** will result in relatively high transmission rates.

  There is evidence that ARV regimens of shorter duration, commencing later than 28 weeks gestation result in higher rates of HIV transmission because they do not adequately cover the antenatal period and result in less viral suppression at delivery.A further key underlying factor associated with inadequate duration of ARV therapy is a high rate of **IUGR and Low Birth Weight** (UGA and preterm) pregnancies.[36] As clinical and sonographic gestational age determination is unreliable after 20 weeks gestatation, HIV positive women who book late are often of uncertain gestation.

  IUGR results in an under estimation of gestation with ARV's starting later than recommended thus shortening ante-natal ARV exposure. Preterm delivery prior to ARV exposure or with shortened ARV duration may reduce efficacy. As the current protocol prescribes commencement of dual therapy at 34 weeks gestation, these patients are more likely to deliver within 2 weeks of commencing ARV's and will have shortened PMTCT cover.

  This emphasises the need for early pregnancy tests and early access to adequate ANC (as recommended in 1. below)**.**

  ANC accessed late or with **IUGR** particularly **limits access to HAART** (for patients who qualify) which needs at least 2 weeks therapy prior to delivery for optimum efficacy, but requires the process of adherence assessment and counselling before commencement thus requiring referral before 34 weeks gestation.

- **cost -** predicted total **cost** vs finite budget allocation. Politics of drug pricing
- **safety -** potential for **toxicity**, **resistance** or adverse reaction in mother or fetus/infant. A factor limiting universal use of HAART as a PMTCT intervention is significant toxicity in patients with high CD4 counts in South Africa[1]
- **regimen complexity -** HAART drugs may require complicated dosing schedules or need refrigeration.

Inadequate budget, substandard logistics and inconsistent drug supply all adversely affect **compliance** but the most important factor underlying poor compliance is **poor quality adherence counselling** and **insufficient treatment support**[2]. Potential **toxicity** and poorly tolerated complex drug regimens will result in lower rates of PMTCT acceptance and contribute to low **compliance**. Patients need to be prepared for potential side effects. Drugs with high potential for viral drug resistance might compromise subsequent HAART.

"Upstream" of these immediate determinants are **underlying** patient, health system, household and community factors. These include illiteracy, concealment of status,

36 Saving Babies 2003, MRC…

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lack of domestic support, fear of stigma and discrimination, deficient power infrastructure and no refrigeration facilities. HAART delivery capacity is improving but is not yet reaching all pregnant women who meet HAART entry criteria. Lack of capacity to perform any more elective Caesarean Sections and prolonged labour results in increased duration of ruptured membranes which increases intra-partum vertical transmission.

Under pinning these are more basic factors determined at local, provincial and national government level (budget constraints, inefficient administration, poverty, unemployment, inaccessible health care, poor transport infrastructure, a mobile population and an under developed PMTCT communication interface with neighbouring provinces.)

4. Late infant PCR testing

HIV infected infants may become ill or die before testing if infant testing is delayed. Rapid progressors may die before testing at 14 weeks of age thus compromising both care and accurate audit of transmission rates.

Late infant PCR testing is an important determinant of Sub-optimal Paediatric HIV management and is dealt with further in section 9. a and b below.

5. Unsafe infant feeding policy

"The success and availability of antiretroviral drug interventions that reduce in-utero and intrapartum transmission of HIV have shifted the focus to identifying interventions that will reduce postnatal transmission of HIV through breast milk"[3].

Breastfeeding may contribute an extra 14 - 28% of HIV transmission between mother and child [4].depending on factors such as viral load, duration and exclusivity of breast feeding, breast pathology and maternal treatment status.

In developing countries breastfeeding has been shown to protect against death from diarrhoea and pneumonia.[5] [6] [7] An officially sanctioned free formula feeding policy runs the risk of producing a negative "spill over" effect[8] on the non-HIV exposed infant population who might be vulnerable to infection, malnutrition and increased mortality if not breastfed. Recent data suggests that although exclusive breast feeding

3Tanya Doherty, Mickey Chopra: South African Health Review, 2006, Health Systems Trust

4 Nnduati R, John G, Bori-Ngacha D, Richardson B, Overbaugh J, Mwatha A,, et al Effect of Breastfeeding and Formula Feeding on Transmission of HIV-1: A Randomized Clinical Trial. JAMA 2000 Mar 1; 283(9):1167-1174.

5 WHO Collaborative Study Team on the Role of Breastfeeding on the Prevention of Infant Mortality. Effect of breastfeeding on infant and child mortality due to infectious diseases in less developed countries:pooled analysis:
Lancet 2000 Feb 5;355(9202):451-5.

6 Victora CG, Smith PG, Vaughan JP, et al. Evidence for protection by breast-feeding against infant deaths from infectious diseases in Brazil. Lancet. 1987;2:319–322.

7 2 Jones G, Steketee RW, Black RE, Bhutta ZA, ¸Morris SS, Bellagio, Child Survival Study G. How many child deaths can we prevent this year? Lancet 2003 Jul 5; 362(9377):65-71.

8 Coutsoudis A, Goga AE, Rollins N, et al. Free formula milk for infants of HIV-infected women: blessing or curse? Health Policy Plan. 2002;17: 154–160.

is well initiated in health care facilities, it is not maintained for very long in the community.

HIV exposed infants (both infected and not infected) who are formula fed have been shown to have higher rates of death, pneumonia and diarrhoea, a faster rate of HIV progression and poorer nutrition in the first 6 months of life than those that are breast fed.[9] There is therefore the very real danger that the gains of preventing mother to child transmission (MTCT) may be undermined by higher rates of death and illness from these causes. The same studies have however shown that the rate of **HIV free survival at 2 years is similar** in the breast and formula fed groups. What is remarkable in the Botswana Study (Mashi) is the powerful protection from early death (< 7 months) that exclusive breast feeding confers on the HIV infected group [rate difference 4,4;95%CI 1,5 – 7,4].[10] This in a group particularly susceptible to early mortality.

WHO recommends avoiding replacement feeding only when it is acceptable, feasible, affordable, sustainable and safe[11]. It is rare that all these pre-requisites are met in many communities in the Western Cape today.

The immediate determinants of **unsafe breast feeding** are

- high viral load
- **mixed feeding**
- mastitis, breast abscess, cracked nipples (high viral load in breast milk)
- infant mucosal damage with mixed feeding or oral thrush

The immediate determinants of **unsafe replacement feeding** are

- **mixed feeding**
- absence of fridge and kettle
- Incorrect or unhygienic formula milk preparation

Factors **underlying** the immediate determinants of unsafe feeding are

- ***inadequate feeding counselling and education***
- ***feeding choice counselling inadequately prescribed in PMTCT protocol***
- ***Uninformed feeding advice***
- ***Sub-optimal maternal treatment status***
- ***high background infant mortality rate***
- access to quality child health services
- the “perverse incentive” of free formula
- lack of sanitation, clean water supply and electricity
- lack of disclosure and poor family support
- “hidden” expenses of replacement feeding to the family
- significant expense of free formula milk to the state

9 Mbori-Ngacha D, Nduati R, John G, Reilly M, Richardson B, Mwatha A, et al.Morbidity and mortality in breastfed and formula-fed infants of HIV-1-infected women: randomized clinical trial. JAMA 2001 nov 21; 286(19):2413-20.

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Under pinning these immediate and underlying factors, are issues of local and provincial incapacity to provide services, overcrowding, poverty and rapid population growth in peri-urban informal settlements.

In addition there are certain knowledge gaps (e.g. Is breast feeding safe if nursing mother is on ARV's ?; Are Pasteurised or donor EBM protocols implementable in the community ? What are district specific mortality rates ?) ? Studies are currently underway which might clarify these issues

6. Maternal death

Poor maternal nutrition and health result in adverse pregnancy outcomes including maternal death.

Table 1.2. HIV status of maternal deaths 2002-2004

	2002-2004	
HIV Status	N	%
Positive	1226	36.0
Negative	351	10.3
Unknown	1829	53.7

[12]

Several studies have linked maternal death to increased subsequent child mortality rates both in the HIV and non-HIV contexts.

The determinants of maternal death have their roots in management of Adult HIV and Reproductive health issues and will not be discussed in detail here.

b. Interventions to optimise PMTCT

1. Reproductive planning and early pregnancy determination for HIV positive women

Some studies suggest it is important to have a viral load below the limits of detection before considering pregnancy and in this regard it is important for family planning services to address the reproductive needs of HIV positive couples. [13]

Pregnancy in HIV infected women should ideally be **planned**[14] with **early pregnancy confirmation** allowing **first trimester access** to HIV testing (VCCCT),

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13 Chen JL, Philips KA, Kanouse DE, Collins RL, Miu A. Fertility desiresand intentions of HIV-positive men and women. Fam Plann Perspect.
2001;33:144-52, 165.

14 Reproduction Decision Making for Couples Affected by HIV: A Review of the Literature Alice C. Thornton, MD, Frank Romanelli, PharmD, Jana D. Collins, BS Reproduction Decision Making Volume 12 Issue 2 May/June 2004Review

Obstetric, PMTCT and Pregnancy Termination Services. Promote and strengthen Family Planning Services while respecting the reproductive rights of HIV positive women. Emphasise barrier contraception in addition to hormonal and other methods. Negative pregnancy test allows opportunity for reproductive counselling and contraception and referral of HIV positive patients to HIV wellness care programs or ARV treatment centres. Positive pregnancy test allows opportunity for early booking bloods and PMTCT counselling and referral for appropriate management.

Develop and promote community based affordable, accessible pregnancy determination service within Family Planning and Sexual Health Services building on existing community based infrastructure.

Promote a culture of a right to early pregnancy determination and antenatal care (Education campaign).

Strengthen Family Planning Service links to Obstetric, PMTCT and Termination of Pregnancy Service. (If CCVT and initiation of PMTCT processes occurs at Family Planning and Sexual Health Clinics, the workload will be reduced at the overstretched Midwife Obstetric Units.)

Early pregnancy determination allows accurate gestational aging, timeous CCVT, CD4 count testing, referral for adherence counselling and sufficient HAART duration to optimise PMTCT effect. Dual therapy also shown to be more effective when commenced at 28 weeks gestation**. This impacts positively on Obstetric and PMTCT decision making and care resulting in better pregnancy outcomes.**

Early pregnancy determination is an intervention with significant potential synergy with Obstetric services as there is much robust evidence linking good antenatal care to better pregnancy outcome.[15] Gestational age is often uncertain with "late booking." Gestational age considerations are often critical to perinatal obstetric decision making Significant improvements in maternal health, PMTCT and pregnancy outcome can be expected from accurate early gestational age determination.

2. Increase acceptance of HIV testing

HIV testing is an important entry point into the PMTCT program.

Ideally HIV status should be known prior to entry to antenatal care (testing before pregnancy at FP and STD services or at early pregnancy determination clinics with referral links to PMTCT and TOPS.)

Strong beliefs about the benefits of testing, knowledge about vertical transmission, the availability of an effective intervention, perceived provider endorsement of testing, and social support all have been shown to contribute to testing acceptance.[16]

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16 **Acceptance of HIV testing during prenatal care. Perinatal Guidelines Evaluation Project.** M I Fernández, T E Wilson, K A Ethier, E B Walter, C L Gay, and J Moore Public Health Rep. 2000 Sep–Oct; 115(5): 460–468.

Confidentiality, counselling and consent remain the principles underpinning HIV testing as endorsed by the WHO. Testing may be client initiated or provider initiated.

WHO recommends that: " A **routine offer** of HIV testing by health care providers should be made to all patients being:

- assessed in a **sexually transmitted infection** clinic or elsewhere for a sexually transmitted infection.
- seen in the context of pregnancy - to facilitate an offer of **antiretroviral prevention of mother-to-child transmission**

Routine universal "compulsory" counselling and voluntary testing (**CCVT)** services as opposed to voluntary counselling and testing (VCT) in these and other health care settings have been shown to result in higher testing rates and therefore more patients with known HIV status early in pregnancy. Robust and clear lines of communication are necessary to avoid duplication of services and unnecessary health care resource expenditure.

Extra counsellors need to be trained and deployed. They should be recruited from the communities they serve. They need a *clear career path with pay progression* according to the extent of their training which could be modular (even distance learning) with modules being: *Sexual health promotion, Reproductive Planning, Basic HIV education, CCVT, PMTCT, Feeding Choice Advice Counselling, Community Based Feeding Support, Adherence, Infant Testing, Child Health Promotion, Nutrition and Growth monitoring,* etc.

If their brief is expanded in this way and they are integrated into the maternal and child health care system, they could form the backbone of a robust Community Health Worker Service. This would have positive spin off way beyond PMTCT and HIV and might well impact positively on the other main causes of childhood mortality.

They should have sufficient private counselling space and regular debriefing to avoid "burn-out".

There are concerns that the recent call for "Opt Out" testing[17] might infringe basic human rights but it would also serve to demystify and de-exceptionalise HIV. It would certainly result in higher testing rates but might drive clients who fear testing from the health care they need and might even reduce uptake of antenatal care.

"*In 2003, the CDC reiterated its goal of universal HIV testing of all pregnant women and recommended the "opt-out approach" to prenatal HIV screening as a useful in perinatal HIV transmission. With the "opt-out" approach, pregnant women are notified about perinatal HIV transmission and its prevention and advised that an HIV test will be included in the standard battery of prenatal tests unless a woman refuses".*

With the "opt-out" approach, pregnant women are notified about perinatal HIV transmission and its prevention and advised that an HIV test will be included in the standard battery of prenatal tests unless a woman refuses".

[17] Is it time to change our testing policies in health care facilities? Personal View. L-G Bekker, R Wood; December 2006, Vol. 96, No. 12 **SAMJ**

This would require significant policy and legislative change at national level and, provided the necessary protocols and support networks are in place, may serve to "normalize" HIV. While the move away from counselling and voluntary testing would be less human resource intensive it might result in lost opportunities for support and education. The temptation to 'skimp' on adequate counselling may also be great in an overworked health care setting.counseling.

"Acceptance rates during pregnancy can be increased when women "understand the modes of vertical transmission and the role of medication regimens in preventing transmission; believe that prenatal identification of HIV can promote the health of mother and child; and perceive their providers as strongly endorsing testing."[30] It is therefore clear that there are many potential benefits that flow from a robust PMTCT counselling service.

Access to community based peer support groups reduces isolation, fear of stigma and encourages domestic disclosure.
Other areas of counselling that need to be explored and developed include partner and couple counselling,which might encourage disclosure which Jackson et al[18] suggest is critical to sustained safe feeding behaviour.

Testing during labour can be linked to beneficial health care intervention – ARV prophylaxis prior to delivery and in the early neonatal period.

Failing this, all un-tested patients delivering before CCVT is possible should have urgent CCVT within 48 hours of birth and if they test positive, their babies should receive post exposure prophylaxis.

3. Optimise ARV protocols

Choice of ARV protocols should be determined by proven efficacy, ease of implementation and safety in terms of toxicity and potential development of drug resistance. As evidence points to transmission risk being highest in patients with CD4 counts less than 250 and the risk of toxicity less, it is reasonable to earmark this group for HAART.

Universal HAART as a routine PMTCT intervention is still logistically and ethically problematic though it may be a medium to long term goal.

The Western Cape's current **dual therapy approach with targeted HAART** is most probably appropriate as it targets patients with highest viral load most at risk of MTCT while providing proven therapy to those at lower risk of MTCT.[19]

It also avoids significant risk of adverse effects of HAART in patients with CD4 counts higher than 250[20]. Referral for adherence counselling and HAART should be fast tracked as soon as CD4 count is known or the patient meets clinical criteria for

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augmented PMTCT (HAART). The threshhold for elective or emergency Caesarian section also needs to be low for high risk patients. The major rate limiting factor for this would most probably be capacity. Enhanced counselling services and the development and implementation of community/family based treatment support using a similar model to the TB DOTS program might ensure better compliance. The potential synergy is obvious with TB/HIV comorbidity.

Dual therapy and avoidance of breast feeding has been shown to reduce transmission to less than 2 % in a 2004 study in Thailand. The current Western Cape transmission rate is 6,1% but it is only 3% in Khayelitsha, the district with the longest running dual therapy program, suggesting that this approach is meeting with considerable success.

Antenatal HIV transmission (5 – 10%) begins to be significant by about 28 weeks gestation[21] while transmission during labour and delivery contributes a further 15% without intervention.

This needs to be taken into account and it is therefore important that ARV's begin at about 28 weeks to prevent the antenatal component of MTCT.

These are the immediate determinants of the effectiveness of the ARV regimen

Community based primary level, accessible good quality sexual and reproductive health services, pregnancy planning, early pregnancy determination and testing, early ANC, early PMTCT and a robust counselling and advisory service all underlie the effectiveness of the ARV regimen employed.

Further upstream, an adequate budget, good logistical support, and a regular sustainable drug supply all further determine the success of the ARV regimen. Furthermore, there needs to be a clear, concise **protocol driven referral chain to secondary and tertiary care** to support the program at community level. Compliance depends on patient education to promote disease and drug process understanding, develop empowerment and be part of decision making and encourage partner testing, disclosure, acceptance and family and community support.

Political and financial support are fundamental to ARV implementation. Leaders should promote the program rather than continually fuelling fears of toxicity. It would be further helped if media coverage of denialist and alarmist ideology was limited

New ways of reducing incidental NNRTI resistance need to be explored (eg . Can maternal dose of NVP be omitted when dual therapy patient has received more than 2 weeks of AZT?)

4. Early PCR testing

Apart from the considerations in C. below, PCR testing at 4 – 6 weeks of age allows better follow up and facilitates audit of the transmission rate outcome of PMTCT. In addition, the shorter wait for infant HIV status determination is more humane and informs subsequent feeding and management choices. [See section C. a. below: Care of HIV infected children]

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5. Safe infant feeding policy

In developing countries breastfeeding has been shown to protect against death from diarrhoea and pneumonia.[22] [23] Perinatally HIV exposed infants who were exclusively breast fed up until 6 months of age in Kwazulu/Natal were shown to have similar rates of virus transmission in the short term as exclusively formula fed infants in a large randomised trial of vitamin A supplementation.[24]

In recent large, randomised studies in Kenya and Botswana, HIV exposed infants (both infected and not infected) who were formula fed were shown to have higher rates of death, malnutrition, pneumonia and diarrhoea, a faster rate of HIV progression and poorer nutrition in the first 6 months of life than those that were breast fed.[25] [70]

There is therefore the very real danger that the gains of preventing mother to child transmission (MTCT) may be undermined by higher rates of death and illness from these causes. The same studies have however shown that the rate of **HIV free survival at 2 years is similar** in the breast and formula fed groups. What is remarkable in the Botswana Study is the powerful protection from early death (< 7 months) that exclusive breast feeding confers on the HIV infected group [rate difference 4,4;95%CI 1,5 – 7,4].[26] This in a group particularly susceptible to early mortality. Infant Zidovudine prophylaxis for the duration of the breast feeding period did not appear to protect against HIV transmission.

There is a real danger that the child health gains from programs promoting breast feeding are eroded by the message implicit in official endorsement of formula feeding in newborns.

The aim of feeding policy in these vulnerable populations should be to ***reduce the risk of HIV transmission during breast feeding while retaining its benefits*** thus reducing the burden of morbidity and mortality associated with formula feeding.

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22 WHO Collaborative Study Team on the Role of Breastfeeding on the Prevention of Infant Mortality. Effect of breastfeeding on infant and child mortality due to infectious diseases in less developed countries:pooled analysis: Lancet 2000 Feb 5;355(9202):451-5.

23 Victora CG, Smith PG, Vaughan JP, et al. Evidence for protection by breast-feeding against infant deaths from infectious diseases in Brazil. Lancet. 1987;2:319–322.

24 Coutsoudis A, Pillay K, Spooner E, et al. Influence of infant-feeding patterns on early mother-to-child transmission of HIV-1 in Durban, South Africa: a prospective cohort study. South African Vitamin A Study Group. Lancet. 1999;354:471–476.

25 Mbori-Ngacha D, Nduati R, John G, Reilly M, Richardson B, Mwatha A, et al.Morbidity and mortality in breastfed and formula-fed infants of HIV-1-infected women: a randomized clinical trial. JAMA 2001 nov 21; 286(19):2413-20.

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26 Ibou Thior, MD, MSc; Shahin Lockman, MD, MSc; Laura M. Smeaton, MSc; Roger L. Shapiro, MD, MPH; Carolyn Wester, MD; S. Jody Heymann, MD, PhD; Peter B. Gilbert, PhD; Lisa Stevens, MD; Trevor Peter, PhD, MPH; Soyeon Kim, DSc; Erik van Widenfelt, BSc; Claire Moffat, MBChB, MPH; Patrick Ndase, MBChB; Peter Arimi, MBChB; Poloko Kebaabetswe, PhD; Patson Mazonde, MBChB; Joseph Makhema, MBChB; Kenneth McIntosh, MD; Vladimir Novitsky, MD, PhD; Tun-Hou Lee, DSc; Richard Marlink, MD; Stephen Lagakos, PhD; Max Essex, DVM, PhD; for the Mashi Study Team. Breastfeeding Plus Infant Zidovudine Prophylaxis for 6 Months vs Formula Feeding Plus Infant Zidovudine for 1 Month to Reduce Mother-to-Child HIV Transmission in Botswana A Randomized Trial: The Mashi Study. JAMA. 2006;296:794-805.

With much vigorous disagreement amongst experts, a sub-optimal feeding counselling curriculum and a Draft National HIV and Infant Feeding Policy[27] that has apparently not made progress since February 2003 it is no surprise that PMTCT counsellors at the coal face have difficulty with this part of the program and largely just leave the choice to the mother.

Furthermore the provision of free formula to mothers is an incentive to take this choice as there is no equivalent material incentive to exclusive breast feeding.

In addition, the counsellors are not necessarily empowered to make an assessment of individual circumstances and give feeding choice advice rather than counselling alone. Studies have shown that healthcare provider opinion strongly influences feeding choice[28]

It is important that the feeding component of PMTCT and Paediatric HIV management program is tailored to accommodate local and individual circumstances and that the outcomes (morbidity and mortality) are audited regularly and programs updated and strengthened on an ongoing basis.

Counselling and nutritional support should commence ante- natally and continue post-natally throughout infancy. Dependable supply of formula milk. Nutrition monitoring. Ensure dependable formula supply and delivery infrastructure. Allow patients to purchase the formula of their choice should they have the means.

Recommendations

1. Establish funding to develop infant feeding counselling service.

2. Employ and train more counsellors (potential synergy with nutrition program)

3. Develop an appropriate discrete PMTCT infant feeding counselling curriculum content that is based on current research applicable to local circumstances.

4. Development of a simple individualised feeding choice decision assistance tool **(Feeding choice assistant)** which would take into account factors such as background infant mortality rate, viral load, domestic disclosure, sanitation, water and power supply, income and housing/income security. This would assist counsellors to objectively individualise feeding advice (as opposed to counselling)

5. Specifically prescribe repeated times of infant feeding counselling in the protocol and flow charts.

6. Audit morbidity and HIV free survival as indicators.

7. Remove bias from feeding decision by providing 6 months free formula to exclusive breastfeeders from the time of weaning.

27 National Dept of Health: Prevention of Mother to Child Transmission of HIV Infant Feeding Policy Draft February 2003.

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8. Establish district specific infant mortality and morbidity rates.

Enhance and develop nutrition monitoring and support service at baby clinics with clinic staff, NGO and community health worker involvement**. The training and deployment of feeding counsellors could be key to the success of this intervention** and holds significant potential to enhance other aspects of child health including reducing clinic work load by performing certain mechanical functions such as weight checking.

6. Maternal survival and care of orphans

The Ugandan government's policy is not to institutionalize orphan care. Instead, guidelines have been developed to promote the care of orphans with the support of the numerous nongovernmental organizations that operate with strong community and family links.

In addition to **HIV-free survival** of children with minimal morbidity, optimisation of maternal health and parental survival are key outcomes which may be compromised by inadequate links or access to. Maternal nutrition and income.
Maternal nutritional support and development of community based employment, income and food generating projects. NGO's Community consultation, Participation and Control/management

B. Care of HIV Exposed but NOT infected children

Children who are born to HIV-infected mothers (HIV-exposed children) but who remain uninfected are a vulnerable group because they have demonstrable immune abnormalities which may place them at a greater risk for childhood infections.[29] Furthermore, these children grow-up in economically vulnerable households among HIV-infected adults increasing their risk for orphaning, food insecurity, under-nutrition and infections including tuberculosis. Their health and care is therefore influenced by immediate and upstream determinants[30, 31] similar to those affecting HIV infected children.

C. Care of HIV infected children

General

[29]Clerici M, Saresella M, Colombo F, *et al*. T-lymphocyte maturation abnormalities in untreated newborns and children with vertical exposure to HIV. Blood 2000;96:3866-3871
[30]Veenstra N. Economic impact of HIV. Best Practices & Research Clinical Obstetrics and Gynaecology 2005;19:197-210
[31] Oxfam International. Causing hunger: An overview of the food crisis in Africa, July 2006. URL: http://www.oxfam.org (accessed 22 September 2006)

According to a recent comparative analysis of provincial paediatric HAART programmes in South Africa more than 55% of children who need HAART in the Western Cape are actually receiving HAART.[32] The Western Cape has made progress with the decentralisation of paediatric ART management to the most appropriate level of care. As evidence of this the proportion of children receiving ART at the three academic hospitals in Cape Town has declined from 78.4% to 38% between March 2004 and September 2006.[33] Although the situation in the Western Cape is decidedly better than many other provinces in South Africa, we should be striving to further optimise care. Particular challenges include extending access of early PCR diagnosis throughout the province, implementing nurse-directed pre-HAAART care comprehensively at level-1 institutions across the province and early and appropriate introduction of HAART. The paediatric HIV burden in hospitals remains high. Unpublished data from Red Cross Children's Hospital indicates that despite the success of the provincial paediatric HAART programme 42% of all children admitted to general paediatric beds are HIV-infected[34] and 33-45.7% of all inpatient deaths over the period 2003-2006 were HIV-related deaths.[35] A vulnerable subgroup is very young HIV-infected children. Interim results of a recent survey at Red Cross Children's Hospital showed that 43.1% of all HIV-infected children admitted to the general paediatric wards at Red Cross Children's Hospital were < 6 months old and that > 90% qualified for HAART.[36] An important aspect of addressing the care deficiencies is an in depth understanding of the upstream determinants that impact on service delivery.

Determinants of sub-optimal management

1. Late diagnosis

Late diagnosis is an important factor determining outcome. An analysis of 409 children treated with HAART at Red Cross Children's Hospital showed that the overall survival of children after 12 months was 84% (95% Confidence Interval: 80-87%). Poor predictors of survival included advanced disease (WHO stage 4 disease) and very high viral load (> 1million copies/ml), surrogate markers of late diagnosis.[37] Factors associated with late diagnosis include the current provincial testing policy, caregiver knowledge and the upstream determinants of caregiver knowledge including limited educational opportunities and financial constraints.[38]

2. Poor pre-HAART care

Between April 2004 and December 2006 the paediatric HIV treatment network in the Western Cape focussed on intensifying the PMTCT programme, developing HAART services throughout the province and strengthening treatment capacity through its community outreach programme, whereby clinicians attached to the 3 academic

[32] Meyers T, Moultrie H, Naidoo K, Cotton M, Eley B, Sherman G. Challenges to Paediatric Care and Treatment. J Infect Dis 2007 (in press)
[33] Eley B, Nuttall J. Antiretroviral therapy for children: challenges and opportunities. Annals Trop Paediatr 2007;27:1-10
[34] Eley, B, January 2007, personal communication
[35] A Westwood, personal communication
[36] Finlayson H, Eley B, November 2006, personal communication
[37] Eley B, Davies M, Apolles P, *et al.* Antiretroviral treatment for children. *S Afr Med J* 2006;**96**:988-993.
[38] HIV/AIDS Directorate, Western Cape Department of Health. PMTCT treatment guidelines, 2004, Cape Town

hospitals engaged in training and onsite consultation.[39] The result is that currently 41 clinics throughout the province are treating children on HAART.[40] What remains to be addressed is the treatment of infected children before they require HAART. Few studies have addressed the pre-HAART treatment gap in South Africa. In a survey conducted in 2001, only a third of all clinics in South Africa were administering cotrimoxazole prophylaxis to HIV-exposed children and the majority of clinics providing cotrimoxazole were administering the incorrect dose.[41] Several immediate factors impact on the provision of care including the competing demands of adult care, limited clinic space and privacy, limited knowledge and experience among health care providers, public awareness about the benefits of treatment, caregiver availability and competence, and caregiver literacy.[42] The development of HIV-related services has been constrained by compartmentalisation of services. Current HIV services are delivered independently of the Expanded Programme of Immunisation (EPI), Integrated Management of Childhood Illnesses (IMCI) and tuberculosis programmes. Integration of HIV services with these established programmes should facilitate the provision of pre-HAART care.[43] Furthermore upstream household determinants include family stability, family health and survival, household disclosure and privacy, household food security and nutrition and household coping strategies.[44, 45, 46]

3. HAART failure

The quality of HAART services for children in the Western Cape is relatively good. An unpublished analysis showed that more than 75% of children consistently achieve virological suppression over the first two years of HAART at level-1 institutions in the province.[47] At Red Cross Children's Hospital 69.7% of children are virologically suppressed after 1year of HAART.[48] These achievements are within the range of virological suppression rates recorded in published clinical trials.[49] However, there remains a significant treatment gap. Between 40-45% of children who should be on HAART are not receiving therapy in the province.[50] Several immediate factors contribute to the treatment gap including competing demands of adult care, clinic space and privacy limitations, pharmacy limitations and drug supply, lack of blood taking skills, limited public awareness about benefits of treatment, caregiver availability and competence, caregiver literacy and orphanhood.[51] In a recent survey of paediatric HAART sites in South Africa, health care professional sited clinic space

39 Eley B. Addressing the paediatric HIV epidemic:a perspective from the Western Cape Region of South Africa. Trans R Soc Trop Med Hyg 2006;100:19-23.

40 HIV/AIDS Directorate, Western Cape Department of Health. Western Cape Antiretroviral Treatment Programme monthly report, January 2007

41 Giese S, Hussey G. Rapid appraisal of primary health care services for HIV-positive children at public sector clinics in South Africa. Cape Town: Children's Institute and Child Health Unit, University of CapeTown, 2002. URL: http://www.hst.org.za/uploads/files/phc_hiv.pdf

42 Eley B, Nuttall J. Antiretroviral therapy for children: challenges and opportunities. Annals Trop Paediatr 2007;27:1-10

43 Meyers T, Moultrie H, Sherman G, Cotton M, Eley B. Management of HIV-infected children. In: Ijumba P, Padarath A, Editors. South African Health Review 2006. Durban: Health System Trust, 2006. URL: http://www.hst.org

44 de Waal A, Whiteside A. New variant famine: AIDS and food crisis in southern Africa. Lancet 2003;362:1234-1237.

45 Bachmann MO, Booysen FLR. Health and economic impact of HIV/AIDS on South African households: a cohort study. BMC Public Health 2003;3:14

46 Russell S. The economic burden of illness for households in developing countries: a review of studies focussing on malaria, tuberculosis, and HIV/AIDS. AsmJ Trop Med Hyg 2004;71(Suppl 2):147-155.

47 P Bock, January 2007, personal communication

48 Eley B, Davies M, Apolles P, et al. Antiretroviral treatment for children. S Afr Med J 2006;96:988-993.

49van Rossum AMC, Fraaij PLA, de Groot R. Efficacy of highly active antiretroviral therapy in HIV-1 infected children. Lancet Infect Dis 2002;2:93-102.

50 Meyers T, Moultrie H, Naidoo K, Cotton M, Eley B, Sherman G. Challenges to Paediatric Care and Treatment. J Infect Dis 2007 (in press)

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constraints, inadequate staff training, lack of clinical capacity and a 'fear' of children as the major constraints preventing HIV-infected children from accessing HAART.[52]

In general, adherence is not a barrier to the success of HAART in adults in South Africa.[53] Proportionally, fewer children achieve complete virological suppression relative to adult patients. Immediate factors that contribute to non-adherence and virological failure include regimen complexity, caregiver availability, caregiver competence and literacy. Several household factors may contribute to treatment failure including family stability, caregiver well being and mental health, household disclosure and privacy, food security and nutrition, coping strategies, and energy supply and refrigeration.[54]

Interventions to optimise chronic HIV care

1. Early PCR testing

Currently the PMTCT provincial programme makes provision for HIV DNA PCR testing of all HIV-exposed children at 14 weeks of life.[55] Research has demonstrated that testing is >98% accurate from the age of 4-6weeks onwards.[56, 57] Global, African and National guidelines support the testing of infants from the age of 4-6 weeks.[58, 59, 60] With the introduction of dry spot testing the technical challenges of taking blood from young children have been overcome and testing is technically possible within nurse-driven services.[61] In addition to reducing the age of testing in the province there is a need to extend PCR testing to all young children irrespective of whether or not they have been identified as HIV-exposed through the PMTCT programme and to transform VCT sites so that the testing of children may be offered. Testing must be linked to pre-HAART services to ensure that young HIV-infected children receive optimal care. Research gaps include the impact on upstream determinants on early diagnosis and the effect of public awareness campaigns on testing rates in young children.

2. Optimise pre-HAART care

Randomised clinical trials have demonstrated that specific interventions may reduce morbidity and mortality associated with paediatric HIV infection. In particular, cotrimoxazole prophylaxis may reduce mortality by 43% and hospital admission rate

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53 Orrell C,Bangsberg DR,Badri M,Wood R. Adherence is not a barrier to successful antiretroviral therapy in South Africa. AIDS 2003;17:1369-1375.

54 Martin S, Elliott-DeSorbo DK, Wolters PL, et al.Patient, caregiver and regimen characteristics associated with adherence to HAART among HIV-infected children and adolescents. Pediatr Infect Dis J 2007;26:61-67.

55 HIV/AIDS Directorate, Western Cape Department of Health. PMTCT treatment guidelines, 2004, Cape Town

56 Sherman GG, Cooper PA, Coovadia AH, e. al. Polymerase chain reaction for diagnosis of human immunodeficiency virus infection in infancy in low resource settings. Pediatr Infect Dis J 2006;24:993-997.

57Zijenah LS, Tobaiwa O, Rusakaniko S, et al. Signal-boosted qualitative ultrasensitive p24 antigen assay for diagnosis of subtype C HIV-1 infection in infants under the age of 2 years. J Acquir Immune Defic Syndr 2005;39:391-394.

58 World Health Organization. Antiretroviral therapy of HIV infection in infants and children in resource-limited settings: towards universal access. Recommendations for a public health approach, 2006. URL: http://www.who.int (accessed 19 August 2006).

59 African Network for the Care of Children Affected by HIV/AIDS (ANECCA). Advocacy statement: Early diagnosis of pediatric HIV infection in sub-Saharan Africa, October 2005. URL: http://www.anecca.org (accessed 18 September 2006)

60 Stevens W, Sherman G, Cotton M, Gerntholtz L, Webber L. Revised guidelines for diagnosis of perinatal HIV-1 infection in South Africa. Southern African Journal of HIV Medicine 2006;Issue22:8-14.

61 Sherman GG, Stevens G, Jones SA, Horsfield P, Stevens WS. Dried blood spots improve access to HIV diagnosis and care for infants in low-resource settings. J Acquir Immune Defic Syndr 2005;38:615-617.

by 23%, vitamin A supplementation may reduce all-cause mortality, and vitamin A , and zinc supplementation may attenuate diarrhoea-related morbidity.[62, 63, 64, 65] Furthermore, INH prophylaxis significantly lowers the mortality in HIV-infected children.[66] These measures together with nutritional support, routine childhood procedures such as immunisation, clinical and CD4 monitoring, and the timely referral for / introduction to HAART form the basis of comprehensive pre-HAART care.[67, 68] Pre-HAART care is a major gap in the early care of the HIV-exposed and infected child in the Western Cape. The service-related and upstream factors, which currently limit the comprehensiveness of pre-HAART care should be addressed. The impact of providing pre-HAART care will be greatest on the very young and probably lead to a reduced burden of young HIV-infected children who access cat level 2 and 3 institutions.

3. Optimise HAART

HAART services for children in the Western Cape are well developed. Therefore closing the treatment gap will be difficult. Currently a relatively neglected group of children are those less than 12 months old. In this regard, the WHO has recently published updated global guidelines for treating children with HAART in which the indications for starting children <12months of age were liberalised, encouraging the earlier introduction of HAART. These guidelines should be adopted as soon as possible in the Western Cape.[69] Another vulnerable group that may be contributing to the treatment gap are orphans. Furthermore, a move towards universal HIV DNA PCR testing linked to comprehensive care will probably make the biggest contribution to reducing the treatment gap. This implies that PCR testing should be linked to an activity such as routine immunisation and all children irrespective of whether or not they were part of the provincial PMTCT programme should be offered testing. Adopting an opt-out testing strategy should further enhance the testing coverage.

The WHO in their recent treatment guidelines recommended that where resources exist, individual countries should consider implementing salvage regimens to address treatment failure. This is an important consideration for South Africa. However, the implications including the cost, health care professional training, regimens, logistic and health system factors should be carefully evaluated.[76, 70]

62 Chintu C, Bhat GJ, Mulengu V, et al. Co-trimoxazole as prophylaxis against opportunistic infections in HIV-infected Zambian children (CHAP): a double-blind randomised placebo-controlled trial. Lancet 2004;364:1865-1871.

63 Coutsoudis A, Bobat RA, Coovadia HM, Kuhn L, Tsai W, Stein ZA. The effect of vitamin A supplementation on the morbidity of children born to HIV-infected women. Am J Pub Health 1995;85:1076-1081.

64 Fawzi WW, Mbise RL, Hertzmark E, et al. A randomized trial of vitamin A supplements in relation to mortality among human immunodeficiency virus-infected and uninfected children in Tanzania. Pediatr Infect Dis J 1999;18:127-133.

65 Bobat R, Coovadia H, Stephen C, et al. Safety and efficacy of zinc supplementation for children with HIV-1 infection in South Africa: a randomised double-blind placebo-controlled trial. Lancet 2005;366:1862-1867.

66 Zar HJ, Cotton MF, Strauss S, et al. Effect of isoniazid prophylaxis on mortality and incidence of tuberculosis in children with HIV: randomised controlled trial. Br Med J published online, 3 November 2006; doi: 10.1136/bmj.39000.486400.55

67 Manary MJ, Ndekha MJ, Ashorn P, Maleta K, Briend A. Home based therapy for severe malnutrition and ready-to-use food. Arch Dis Child 2004;89:557-561.

68 Obaro SK, Pugatch D, Luzuriaga K. Immunogenicity and efficacy of childhood vaccines in HIV-1-infected children. Lancet Infect Dis 2004;4:510-518.

69 World Health Organization. Antiretroviral therapy of HIV infection in infants and children in resource-limited settings: towards universal access. Recommendations for a public health approach, 2006. URL: http://www.who.int (accessed 19 August 2006).

70 Eley B, Nuttall J. Antiretroviral therapy for children: challenges and opportunities. Annals Trop Paediatr 2007;27:1-10

Overview and recommendations

The extra burden HIV places on Reproductive and Child Health Care Systems has the potential to severely disrupt existing services and adversely affect health outcomes particularly if resources are diverted from other services or the existing infrastructure is not adapted to cope with the extra load. This is particularly so in the area of infant feeding where officially sanctioned (free) formula feeding is compromising the gains of exclusive breast feeding programs.

However, in this catastrophic epidemic, at this time, there lies an opportunity to improve Women and Childrens' Health Care as a whole.

Stand alone, vertical HIV programs will not be able to achieve these potential gains. There is an urgent need to "de-exceptionalise" HIV and comprehensively incorporate HIV prevention and management programs into the health service as creatively and efficiently as possible to optimise health outcomes in the context of budget constraints and finite resources.

As we have shown, **new resources employed in** the PMTCT and paediatric **HIV** management programs **can impact positively on many aspects of the health care system** if potential synergies are identified and developed. (e.g. Maternal and Child Health, Nutrition, Tuberculosis control, Reproductive and Sexual Health programs).

HIV related programs should bring extra resources rather than extra workload and be integrated into the health care system in a manner that improves efficiency and perhaps even **act as a lynchpin for the revision of the health care system as a whole.**

As HIV/AIDS is a relatively new problem, evidence on the effectiveness of multifaceted programs is limited. There are success stories in Botswana, Uganda, Brazil and India[71] from which we may learn. However, in many respects, it is necessary for the Western Cape (and South Africa) to develop **a novel and creative multi-level, multi-faceted, inter-sectoral approach using the HIV prevention and management program as the lynchpin to reform the child health care sector and to tackle the major causes of child mortality and morbidity.**

[71] **Evaluation of United Nations-supported pilot projects for the prevention of mother-to-child transmission of HIV. United Nations Children's Fund (UNICEF), 2003**

With this in mind we recommend:

Key interventions for the success of PMTCT and Paediatric HIV management programs

At health system level

- ***comprehensive integration*** of the PMTCT program and Paediatric HIV management service into health care systems and structures in facilities that are geographically near the communities they serve. The health districts with the highest child mortality rates should be prioritized in this process. In particular, develop and strengthen links (support, communication and referral channels) between sexual and reproductive health service and child health and nutrition services across primary, secondary and tertiary levels.

- ***Strengthen and develop community based reproductive and sexual health services*** including the promotion of ***reproductive planning services***, an ***early pregnancy diagnosis service*** and ***basic antenatal care including PMTCT initiation*** at clinics within the communities most at risk.

- ***Safe feeding and better growth and nutrition monitoring programs*** by ***robust promotion of background exclusive breast feeding*** as the norm in the general population. ***Link BFHI to the development of Community Based EBF programs–*** note that BFHI is already being linked Better Births Initiative (BBI). Under the auspices of Nutrition Dept, ***promote robust development of feeding counselling*** curriculum, increase capacity to train feeding counselors (prioritise selection of trainees from high risk communities) and deployment in their own communities. ***Upskill them*** *and* ***expand their brief to include feeding risk assessment, individualized feeding choice advice, child health promotion, growth and nutrition monitoring*** especially for high risk children like LBW and those exposed to HIV. Develop *individualized feeding choice assistance tool* [*IFCAT*] to assist PMTCT counsellors to advise patients which feeding choice is safest for them. (also explore pasteurized EBM and Donor EBM options)
- ***Develop and promote case management guidelines for all HIV exposed infants*** along IMCI guidelines. (with support across primary, secondary and tertiary levels along clear protocol driven communication and referral channels but including outreach services)

At an underlying level:

- ***comprehensive parent and child survival and support programs***, including health care (HAART), health facility based birth registration and social services.
- identify ***key empowering community based projects*** to generate employment, food and income possibly with the assistance of NGO's (like M2M2B and Kidz Positive)

At a more basic level:

- ***issues determining equity between Western and Eastern Cape and the resultant population movement*** need to be investigated and addressed – a starting point might be the PMTCT interface between the provinces.
- Delivery of ***housing and services***
- ***Transport and health care infrastructure development to facilitate access*** to health care particularly at a primary level
- human resource development to meet the above needs