# CHAPTER 1 - INTRODUCTION

At the time that the research documented in this thesis was conducted, HIV prevalence among pregnant women in Gauteng Province for 2003 was 29.6%, in 2004 33.1% and in 2005 32.5%.[1] More recently, the 2006 UNAIDS global report indicated that 5.5 million people in South Africa were infected with HIV, representing about 14% of the global burden; one out three South African pregnant women attending antenatal care in public health facilities is HIV-infected and the country accounts for 19% (100,000) of all new mother-to-child transmitted infections.[2] In addition, 13% (294,000) of all HIV infections in children and 10% (1.5 million) of all children orphaned by AIDS are in South Africa.[2]

Given this huge impact of HIV on infant and maternal health, there is now an extensive body of knowledge that has been compiled by South African researchers on mother-to-child transmission of HIV (MTCT) and, in particular, on the trends in infant feeding practices in the HIV context.

HIV infection has an unmeasured effect on a woman's mothering ability towards her newborn baby. The factors that could influence a mother's ability to care for her offspring include: her own disease status and progression[3,4,5], nutritional status[6-8], or depression and other psychosocial issues, like disclosure[9,10,11,12]. Data indicates that the infant's own infection and disease status and progression may also impact on maternal caring capacity[13,14,15].

One of the strategies to improve declining or weak caring capacity among families that are exposed to HIV would be to ensure that HIV-infected mothers are provided with sufficient health care to delay HIV disease progression. Most of the previous international studies conducted on nutritional status and HIV have been conducted in the USA among HIV-infected homosexual males or drug

users.[16,17,18] Recent published studies on nutritional status and HIV in South Africa have had shorter follow-up times and used relatively complex and invasive methods to determine nutritional status.[19]

There are no South African studies that have systematically documented, over a two year period post-delivery, the trends in nutritional status of HIV-infected women. There are even more limited studies that attempt to link nutritional status of postpartum HIV-infected women to measurements of psychosocial wellbeing and to infant feeding practices and health outcomes for their children.

# CHAPTER 2 - BACKGROUND AND LITERATURE REVIEW

## 2.1 HIV AND INFANT FEEDING CHOICES

### 2.1.1. Mother-to-child transmission of HIV

It is estimated that nearly 1800 children worldwide, and especially newborns, contract HIV on a daily basis and, of these children, more than 85% live in Sub-Saharan Africa[2]. The Prevention of Mother-to–Child Transmission of HIV strategy (PMTCT) was adopted globally as a means of addressing vertical transmission of HIV from parent to child, yet in Sub-Saharan Africa to date just less than 6% of pregnant women are offered or receive PMTCT interventions.[2]

In South Africa the annual national antenatal clinic sero-prevalence surveys conducted among pregnant women reported HIV prevalence rates of 27.9%, 29.5% and 30.2% between the years 2003, 2004 and 2005 respectively. However, Gauteng Province, in which the study reported on in this thesis was conducted, was amongst the provinces with higher rates.[1]

Evidence emerged in scientific literature in mid-1996 that HIV can be transmitted though breastfeeding. Since that time several studies have been conducted in developing countries to assess the biological and programmatic implications of HIV transmission through breastfeeding. The estimated risk of transmission is 5-10% during pregnancy, 10-20% during labour and delivery, and 5-20% through breastfeeding.[3]

### 2.1.2. Infant feeding choices and prevention of HIV transmission

At the same time, the dilemma posed by infant feeding options in the context of HIV is that replacement feeding (RF) and its safety can only be assured if strict criteria are met such as affordability, feasibility, acceptability and sustainability (the so-called AFASS criteria)[20]. In most resource-poor settings these conditions are difficult to meet, and avoidance of all breastfeeding carries additional mortality risks. The evidence from a World Health Organization (WHO) meta-analysis indicates that in the poorest countries children who are not breastfed during the first two months of life are six times more likely to die from infectious diseases[21], irrespective of HIV status.

A study from Botswana documented trends in infant feeding practices from the PMTCT pilot sites.[22] In this study, data were obtained from women who were either randomised to formula-feed their infants or to exclusively breastfeed while being given prophylactic zidovudine. Women who chose to formula-feed independently were also followed. In this population, similar to South Africa, exclusive breastfeeding practice is not the norm and hence they found that none of the 31 women assigned to breastfeed did so exclusively for five months. There were also observations that 22% of the women assigned to formula-feed were highly likely to have breastfed starting within the maternity ward and this was confirmed by breast examination results. The authors concluded that none of the breastfeeding-arm mothers ever adhered to exclusive breastfeeding for five months and even those who had been assigned to formula-feed did not do so exclusively. This study thus challenged the global recommendations on infant feeding in the context of HIV as they differed from the normal infant feeding practices inherent in this community.

Before the introduction of simple short-course antiretroviral drug regimens, such as nevirapine (NVP), prolonged breastfeeding contributed to less than a half of

mother-to-child HIV transmissions in the developing world.[3] Currently, prophylactic short-course treatment options are available to reduce mother-to-child-transmission, however, prolonged breastfeeding exposure continues as a leading cause of HIV infection in infants. A clinical trial of 425 women in Nairobi reported that without short-course antiretroviral treatment, breastfeeding for two years or more doubles the overall risk of mother-to-child transmission of HIV to about 40%.[23] Other studies have documented that both the volume of milk ingested and the length of exposure are factors in transmission.[24-26]

Breastfeeding transmission can occur early in the postnatal period or later on. A meta-analysis of data from nine mother-to-child transmission studies involving over 5000 infants has found that 1509 infants were breastfed and that breastfeeding continued for an average of 6.8 months. The number of HIV infections attributed to breastfeeding was 179, giving a transmission rate of 12%. HIV transmission occurred before 4 weeks of age in 64% of cases.[21] Even though it is established that there is a heightened risk of transmission in the postpartum period, a meta-analysis of nine major studies of mother-to-child HIV transmission has shown that there is a significant and sustained risk of late HIV transmission to breastfed children. Of the 4085 children included in the analysis, 42% acquired infection after day 28. The risk of late postnatal transmission continued throughout the breastfeeding period and was relatively constant. The risk for transmission was significantly higher among male infants and infants born to women with low CD4 cell counts.[27]

A study in Botswana compared the efficacy and safety of two infant feeding strategies for the prevention of mother-to-child HIV transmission. All pregnant women received zidovudine 300mg orally twice daily from 34 weeks of gestation and in labour. Mothers and infants were randomised to receive single-dose nevirapine or a placebo. Infants were randomised to six months of breastfeeding plus prophylactic infant zidovudine, or formula-feeding with one month of infant

zidovudine. They found that by the seventh month HIV infection rates were 5.6% (32 infants in formula group) versus 9% infants in the breastfed group. Furthermore, they found cumulative infant mortality at seven months to be significantly higher in the formula group than the breastfed group (9.3% vs 4.9%; p=0.003), but these differences diminished with time and by 18 months there was no significant mortality differences between the two groups.[28]

Exclusive breastfeeding is recommended as a protective option of infant feeding primarily as it provides protection for infants from morbidity or mortality regardless of the HIV status of the mother. Increasingly the literature acknowledges that safe and exclusive breastfeeding among HIV exposed infants is a key intervention contributing to HIV free survival.[61] HIV free survival is a term applied to estimate the number of infants alive and who have tested HIV negative following interventions including safe and exclusive infant feeding, and provision of ARV prophylaxis to prevent mother to child transmission of HIV.

### 2.1.3. HIV and infant feeding policy guidelines

In 1997 the WHO, UNICEF and UNAIDS issued a joint policy statement on HIV and infant feeding which served as the source document for countries to begin to apply infant feeding options for HIV-infected mothers in a practical setting. Subsequently, the WHO and UNICEF first issued international guidelines on HIV and infant feeding as part of PMTCT programmes in 1998.[29] The guidance from this was that HIV-infected mothers should be counselled to completely avoid breastfeeding and if this is not possible, the WHO and UNICEF recommend exclusive breastfeeding (EBF) during the first few months of life. Based on several studies, including a recently published study conducted in KwaZulu-Natal,[30] the WHO and UNICEF have now revised the period of exclusive breastfeeding to six months amongst HIV-infected mothers choosing this feeding option.[31]

The KwaZulu-Natal study[30] was conducted to assess the survival and HIV-transmission risk associated with exclusive breastfeeding and other types of infant feeding in KwaZulu–Natal, South Africa. It consisted of 2722 HIV-positive and HIV-negative pregnant women attending antenatal clinics who were enrolled in a non-randomised intervention cohort study that offered intensive infant feeding support. There were 1372 infants born to HIV-positive mothers and of these mothers 1132 initiated EBF from birth. The median duration of cumulative EBF was 159 days. The estimated risk of postnatal transmission of HIV by 6 months of age in exclusively breastfed infants who were negative at 6 weeks of age was 4%. Mixed feeding before or after 14 weeks nearly doubled the risk of transmission and the addition of solids increased the risk 11-fold. Cumulative three-month mortality in exclusively breastfed infants was 6.1% compared to 15.1% in infants who were given replacement feeds (p=0.051). This study has been cited as being important in providing further clarity on the benefits to early child survival of exclusive breastfeeding among HIV-infected mothers and the risks posed by mixed feeding.

### 2.1.4. Recall bias in estimating exclusivity or duration of infant feeding practices

Research studies on HIV and infant feeding depend on recall of breastfeeding practices in order to establish whether infants are being breastfed exclusively or not. However, recall is highly subjective and may result in bias. A study on infant feeding practices conducted in rural Zimbabwe acknowledged that self-reporting on infant feeding practices has the potential of leading to recall bias especially in recalling the age at which solids were introduced into the diets of the infants.[32]

Recall bias occurs and continues to constitute a potential bias in the data on infant feeding. In an attempt to validate methods of collecting infant feeding

data a study was undertaken in KwaZulu-Natal in 2003 where 130 postnatal mothers were interviewed weekly and, at every interview, a four-hour and a seven-day recall breastfeeding history was taken.[33] A subset of 70 mothers also received two intermediate visits per week during which additional 48-hour recall interviews were conducted. Ninety three infants were revisited at 6 to 9 months of age when mothers' recall of exclusive breastfeeding duration from birth was taken. They found that the reported breastfeeding practices over the previous 48 hours did not reflect exclusive breastfeeding practices since birth (specificity 65-89%; positive predictive value 31-48%) and that six-month exclusive breastfeeding-duration recall was equally poor (sensitivity at two weeks 79%; specificity 40%). Seven-day recall accurately reflected EBF practices compared with thrice weekly recall over the same time period (sensitivity 96%; specificity 94%). The authors concluded by recommending that, in order to minimise recall bias, data on duration of exclusive breastfeeding be collected prospectively at intervals of no longer than one week (seven days).

### 2.1.5. Unsafe formula-feeding

Given the socio-economic conditions under which most HIV-infected women in the developing world live, there is also a substantial risk of bacterial infections when formula-feeding is practiced under unsafe or unhygienic conditions. In a sub-study of the South African National PMTCT Cohort the preparation of formula-feeds by HIV-infected mothers was observed and laboratory analysis was conducted on the samples to assess levels of bacterial contamination.[34] In this study Escherichia coli were isolated from 64% of the milk feeds and Enterococci from 26% and 67% of the samples had at least one of these contaminants. The researchers found less contamination of samples from mothers who cleaned and sterilised feeding utensils for the infants. An additional safety concern identified in this study was over-dilution of 28% of the milk

samples collected at the clinic and 47% of the samples collected in the homes. The risk of over-dilution of feeds was found to be greater for older infants and when there was no access to running water in the house. More recent data on contaminated and over-diluted infant formula-feeds in South Africa has been obtained from rural KwaZulu-Natal.[35]

### 2.1.6. Problems and risks in the PMTCT programme

In South Africa the PMTCT programme, which began in 2001[36], provides two infant feeding options to HIV-infected pregnant women subsequent to pre- and post-test counselling. These options are:

- Exclusive breastfeeding with early cessation. Women who choose to breastfeed are expected to have been counselled on the benefits of exclusive breast feeding for a limited duration up to four months, followed by abrupt cessation.
- Provision of free infant formula for the first six months after delivery.

There has been extensive documentation of the experiences of implementing PMTCT in South Africa since the inception of the programme. One of the first reports was prepared by the Health Systems Trust (HST) and it reported that only about 51% of women agree to test for HIV, with a wide range of uptake figures across sites.[37] Regarding infant feeding, the researchers reported at this time that most women chose to replacement feed (RF) using infant formula, although there was considerable variation across sites. Breastfeeding practice was found to be more prevalent in rural areas. Additional recommendations made by the study group included reviewing the provision of free infant formula as they felt this may contribute to increased mortality and morbidity and may encourage mixed feeding. Alternatively, they proposed that infant formula should

only be availed to those mothers who could afford to do so and all other mothers should be supported to exclusively breastfeed.

Other researchers[38] raise concerns over the possible detrimental effects on child survival by providing free infant formula in the PMTCT programmes, especially in resource-poor settings. They suggested that free infant formula may compromise any woman's sense of reasoning and thus she might be inadvertently coerced into formula-feeding. Further, the researchers warn that it is possible that it will be only the most advantaged groups in society that will benefit from the free formula, therefore there is no assurance of compliance to exclusive formula-feeding by the sero-positive mothers and that there are hidden costs associated with the provision of formula milk.

One of the pre-conditions for the provision of infant formula on the PMTCT programme is that the recipient mothers will have received a detailed counselling session providing information on the merits and demerits of this infant feeding choice. A study in three PMTCT sites in South Africa[39] reported that on average only 18 minutes were spent counselling and that in all sites the counsellors had good communication skills. However, the infant feeding counselling was the weakest component in all sites, with only 35% (12 out of 34) of mothers informed about the risks of HIV transmission by mode of transmission. Frequency of contact between the counsellor and the HIV-infected pregnant mother during antenatal visits and follow-up support on infant feeding practices at the household level have been proposed as ways of ensuring that mothers adhere to their original infant feeding choice and practice safe feeding. [40]

### 2.1.7. Practical considerations in the application of HIV transmission and infant feeding guidelines

Whilst there is sufficient scientific evidence on the risks of breastfeeding and replacement feeding in the HIV context, which has resulted in programmatic

guidance in the PMTCT programmes, there has not always been sufficient consideration of the practical application of these recommendations at household level. It is clear that household and socio-cultural influences remain important determinants of actual infant feeding practices of HIV-infected women. Research conducted in KwaZulu-Natal indicated that women who delivered in hospitals were faced with the immediate dilemma on infant feeding at delivery as most felt that hospital personnel were insisting on breastfeeding, especially in those facilities that are designated "Baby Friendly" (in accordance with the WHO/UNICEF Global Criteria) and that a decision not to breastfeed would amount to public disclosure. Further, it emerged that younger women felt more pressured to breastfeed as the family expected the baby to be constantly breastfed. In this study it was predominantly the mothers aged over 19 that chose to replacement feed.[41]

Pressures from partners and family members on infant feeding choices of HIV-infected mothers have also been documented in the Ivory Coast in 2007[42]. In this study the researchers found that of the 580 women who delivered, 309 (53%) planned to formula-feed and 256 (44%) planned to breastfeed and 15 (3%) had not indicated feeding intent. Adherence to the initial formula-feeding intent in this cohort was over 90%. In terms of actual feeding practice, they found that of the 295 mothers who formula-fed, 93.6% were successful (refrained from breastfeeding) by day two and 84.2% by 12 months, but 15.6% of the formula-feeding group had breastfed their babies at least once. Researchers found that the mothers who hesitated to choose formula-feeding for their infants predominantly feared the partner's reaction (39%) and the family circle reaction (31%), were Muslim and were of low educational level. However, regardless of this there were many more women who chose to formula-feed in this cohort and they were also availed with the equipment to prepare formula feeds safely.

Additional data from a cohort study of three PMTCT sites in South Africa indicates that amongst mothers who had chosen to breastfeed their infants, the decision lay in the entrenched knowledge that breast milk is best and this often outweighed the perceived risk of HIV transmission through breast milk. The study also found that health workers were themselves misinformed on the HIV transmission risk from breastfeeding, resulting in them imparting mixed messages and exerting undue authority over the mothers in terms of infant feeding choices.[43] The same study has reported that an additional challenge in sustaining infant feeding choices in the context of HIV arises when mothers who have selected to replacement-feed their infants run out of formula feeds prior to their next scheduled clinic visit.

Such studies highlight the importance of counselling on HIV and safe infant feeding to all family members but especially to the partners and the health care providers. Data from Khayelitsha, an informal settlement in the Western Cape Province of South Africa, indicated that whilst mothers were aware of HIV transmission through breastfeeding, 90% of them said that this would not impact on their infant feeding decision-making. Healthcare workers who were included in this study, however, were not able to indicate correctly the risk of HIV transmission through breastfeeding and stated that this subject was confusing to them.[45] These findings indicate the challenges health workers experience in counselling women individually on the acceptability, feasibility, affordability, sustainability and safety ( the AFASS criteria) of infant feeding options in the context of HIV. The practical application of these criteria, particularly when counsellors attempt to communicate the balance of risks of either replacement feeding or exclusive breastfeeding whilst imparting accurate information, has proven to be most challenging. In particular, health workers face particular difficulty in communicating the individual components of the AFASS criteria. These difficulties ultimately contribute towards inappropriate choices of infant feeding practices on mortality as reported by Jackson et al.[24]

### 2.1.8. Practical issues associated with early cessation of breastfeeding

As previously mentioned, the South African PMTCT protocol states[36] that those mothers who select to breastfeed their infants should do so for a limited period of time, followed by early or abrupt cessation, provided adherence to the AFASS criteria can be assured for replacement feeding.

A study in the Ivory Coast[45] assessed the uptake of a nutrition intervention that promoted exclusive breastfeeding with early cessation which was set at between 3 and 4 months of age and also offered replacement feeds as a means of reducing postnatal HIV transmission. Mother-infant pairs in this study were followed up for two years and provided with nutritional counselling. Of the 557 mothers enrolled, 262 (47%) initiated breastfeeding with the probability of practicing exclusive breastfeeding from birth being 18% and 10% at 1 and 3 months of age respectively. Complete cessation of breastfeeding was obtained in 45% and 63% by 4 and 6 months of age respectively. They found that societal and family pressures, such as living with a partner's family, were associated with failure to achieve early cessation of breastfeeding.

In reviewing issues, risks and challenges of early breastfeeding cessation as a means of reducing postnatal transmission in Africa, researchers call for caution as the practice of early and abrupt breastmilk cessation is not as yet entrenched within the cultural feeding norms on the Continent and thus its implementation may need to be done cautiously. They further mention that one of the risks associated with abrupt cessation of breastfeeding is psychological trauma for both mothers and infants and potential mastitis in the mothers.

In a qualitative study in Nigeria[47] HIV-infected respondents did not anticipate that early cessation of breastfeeding would be problematic as the mother would have at least provided her newborn with some of the protection provided from breastfeeding.

From this review it is apparent that in African populations a decision to avoid breastfeeding among HIV-infected women is made complex by the family situation, health worker bias in the counselling sessions, practical challenges posed by infant formula preparation and a difficulty in translating the AFASS criteria into practice when selecting the infant feeding method. Furthermore, even amongst those HIV-infected women choosing to breastfeed, adherence to exclusive breastfeeding followed by rapid cessation does not appear to be easy to implement practically at household level.

### 2.1.9. Maternal viral load and mastitis as risk factors for HIV transmission

An additional risk factor to increased HIV transmission through breastfeeding is poor maternal health, which includes a mother's own disease state, levels of immune factors in the breast milk and possible breast pathologies or abnormalities, such as cracked nipples and mastitis.[48,49,50]

Researchers investigated the determinants of RNA viral load among HIV-infected women and the effects on infant feeding and mastitis. Samples of breast milk were obtained from 145 HIV-infected breastfeeding mothers at one, six and 14 weeks postpartum and measurements of the sodium/potassium ratio in the milk was used as an indicator of mastitis. There was a variability of between 13% and 26% in milk viral load in the first 14 weeks. They also found that low blood CD4 cell counts (<200cells/mm$^3$) during pregnancy and elevated sodium potassium ratio was significantly associated with increased levels of milk RNA viral load. It

was concluded that whilst breast milk RNA viral load varied in the first 14 weeks postpartum, elevated levels were associated with sub-clinical mastitis and severe maternal immuno-suppression [51]. The findings of this study together with those from other research[52,53] placed further emphasis on the importance of maintaining optimal breast health in the context of HIV and this may be achieved with sufficient counselling on lactation management being provided to HIV-infected mothers.

More data on the contribution of maternal viral load and low CD4 cell counts to HIV transmission comes from Tanzania. It has been reported that infants who are not infected at birth have a 4% risk of contracting HIV at 4 months and an 18% risk of HIV infection at 2 years if they breastfeed.[54] Provision of antiretroviral therapy during breastfeeding, together with adequate lactation management could be possible interventions for preventing vertical transmission of HIV through breastfeeding.

### 2.1.10. Breastfeeding and maternal outcome

The concern over maternal health and nutritional status especially during the postpartum period has been particularly driven by the findings from Nairobi, Kenya[23], which indicated that HIV-positive mothers had higher mortality rates if they breastfed their infants. These results arose from a secondary analysis of a randomised trial of breastfeeding compared with formula-feeding conducted in Nairobi, Kenya between 1992 and 1998. The trial was designed to assess the rates of mother-to–child transmission of HIV according to mode of infant feeding. Eighteen of 197 women randomly allocated to breastfeed their infants died within 24 months of delivery compared with six of the 200 women allocated to the formula-feeding group. The cumulative 24-month mortality rates were 11% and 4% respectively, corresponding to a 3.2-fold higher risk of death (95% confidence interval [CI]: 1.3–8.1).

The researchers suggested that the demands of breastfeeding in HIV-infected mothers might accelerate the progression to HIV-related death. However, this finding was not consistent with studies examining exclusive breastfeeding, which have not found higher death rates in breastfeeding women.[50] Furthermore, prospective studies in Tanzania[54] and Zambia[55] found no evidence that breastfeeding was detrimental to the health of HIV-positive mothers, except among mothers with advanced HIV disease and severe immuno-suppression.

Eleven percent (11%) of children and 3% of mothers died. This is comparable to a study in Malawi which found that of the 2000 HIV-infected women, 2.2% had died and 15.5% of their children had died during a two-year follow-up period. The median duration of breastfeeding in this cohort was 18 months, exclusive breastfeeding was two months and mixed feeding was 12 months. This study did not find any association between breastfeeding and maternal mortality or morbidity, even after adjusting for maternal viral load and other covariates.[4] Instead, it was found that breastfeeding was associated with significant reductions in mortality among the children born to HIV-positive mothers. This protective effect of breastfeeding could be from the immunological and anti-bacterial factors in breast milk.

More recently, a study from Kenya documented over a two-year period HIV-1 disease progression in breastfeeding and formula-feeding mothers.[5] This study was undertaken to further substantiate the earlier findings in Kenya[23] on the three-fold increase in mortality risk that was associated with breastfeeding. Mothers in Nairobi were allowed to self-select whether to breastfeed or formula-feed their newborns and they were followed-up for a period of 24 months postpartum to assess CD4 counts, HIV-1 RNA levels and Body Mass Index (BMI). Thirty three percent of the 296 women elected to formula-feed and 67% chose to breastfeed. Women most likely to formula-feed were more educated and had

a flush toilet at home and had reported a history of HIV-1-related illness. At 36 weeks of gestation, which was the baseline assessment in this study, there was no significant difference between the formula-feeders and breastfeeders. Changes in CD4 cell counts, HIV-1 RNA levels and BMI between 32 weeks of gestation and one month postpartum were not significantly different by feeding choice.

Overall, the researchers found that CD4 cell counts declined 3.9cells/µl/month between month one and 24 ($p<0.001$) and CD4 cell percentages declined 0.11% per month ($p<0.001$). They found that the mothers who continued breastfeeding had a significantly higher rate of CD4 cell count decline than did those who had breastfed for a shorter time (-7.7 vs -4.4cells/µl/month; $p=0.014$). After cessation of breastfeeding, former breastfeeders were found to have a significantly lower rate of CD4 cell count decline (-3.2cells/µL/month) than current breastfeeders ($p=0.003$) and a rate similar to that of never breastfeeders ($p=0.3$). Mortality was significantly associated with baseline CD4 count (hazard ratio [HR] of 2.7 per 100-cell/uL; $p<0.001$). Women with baseline CD4 cell counts <200 cells/µL had a HR of 1.7 ($p=0.002$) for death during the two–year follow-up period. They concluded that whilst breastfeeding may accelerate the decline in CD4 cell counts, it did not have a long-term effect on HIV-1 RNA level or mortality.

The most significant decrease in CD4 cell counts was between months one and 24 postpartum (estimated decrease of 3.9cells/µL/month or 48cells/µL/year). CD4 cell count decline was highest among current breastfeeding women (-7.7cells/µL/month) and this was significantly higher than for formula-feeders (-4.4cells/µL/month) and for women who ceased breastfeeding, the rate of CD4 cell count decline was -3.2cells/µL/month. This implies that there is a mechanism that spares the decline in CD4 cells count once lactation ceases. From the study findings it was deduced that the accelerated CD4 cell count decline during

breastfeeding could result from hormonal changes, nutritional and metabolic changes or the numeric loss of CD4 cells as part of the process of breastfeeding.

The researchers state that the levels of CD4 cell count decline they observed, whilst statistically significant, may not be clinically relevant especially for women who breastfed for short periods of time. The CD4 cell count decline in women who breastfed for six months did not differ significantly from the decline in those who never breastfed. There was no difference in mortality in the formula or breastfed groups and it is possible that the women were less immuno-compromised to start off with in both groups. It would therefore appear that although breastfeeding may affect CD4 cell count and BMI in HIV-1 infected women with extended maternal care, breastfeeding is not necessarily associated with a significant decline in maternal health. The authors conclude that their data therefore supports the recommendation by the WHO that women who are HIV-infected and choose to breastfeed should do so for six months as it appears breastfeeding has minimal adverse effect on maternal CD4 cell count.

Another meta-analysis[21] which used data from HIV-1 infected women has found no differences in mortality between HIV-positive mothers who breastfed compared to those who never did after 18 months. However, amongst the women who did start breastfeeding, the study found a lower risk of death among those who were still breastfeeding after 18 months (HR = 0.05, 95% confidence interval: 0.03;0.09; $p < 0.0001$). This is probably due to the fact that the women who are able to breastfeed for longer are the women who are healthier rather than mortality being affected directly by the mother's choice of feeding method.

### 2.1.11. Infant Feeding practices in South Africa

In South Africa the Demographic and Health Survey (DHS) provides national data on breastfeeding trends. According to the 1998 DHS report[56], whilst breastfeeding continues to be the cultural norm with 88% of South African mothers reported to have ever initiated breastfeeding, the low prevalence of exclusive breastfeeding was a cause for concern. In the first three months of life only 10% of infants were exclusively breastfed. Overall the rate of formula-feeding was 48.3% nationally. Of nutritional concern is that approximately 70% of children in this age category had received complementary feeds before the age of 6 months.

In 2003 the DHS[57] reported that 12% of infants are exclusively breastfed from 0-3 months (a 2% increase from the 1998 SADHS). Only 1.5% are exclusively breastfed at 4 to 6 months, and 28.5% of infants are bottle-fed with a nipple, 6% of babies less than 4 months old and 27% of babies aged 4-6 months are given semi-solid food. It is clear from the data that in South Africa, and indeed in several other African countries, mixed feeding is practiced as the "normal" standard of infant feeding.

Analysis of DHS data from 14 countries has found that in societies where prolonged breastfeeding is the norm women are less likely not to breastfeed and, if they fail to initiate breastfeeding, they are more likely to do so because of preceding morbidity, as compared to societies with shorter median breastfeeding durations.[58]

A separate study among women in rural KwaZulu-Natal found exclusive breastfeeding of very young infants to be uncommon, at a rate of 5%.[59] The low prevalence of the practice of exclusive breastfeeding is a phenomenon that is common in both urban and rural settings alike. Researchers investigated the factors that were conducive to women adhering to their selected infant feeding mode in three PMTCT sites in South Africa. They found that among women who

were able to adhere to exclusive breastfeeding, a firm belief in the benefits of breastfeeding and a supportive home environment were prerequisites. Formula-feeders found this practice easier to adhere to if they accessed electricity, owned a kettle and a flask, which made night feeding easier.[43]

Nevertheless, in the context of HIV, mixed feeding is a high risk behaviour that can result in increased transmission rates. A study conducted in KwaZulu-Natal Province, where 551 women were counselled on the risk of HIV transmission through breastfeeding and offered formula at a subsidised price, found that after 15 months transmission rates were 19% for formula-fed infants, 25% in exclusively breastfed infants, and 35% in mixed-fed infants. The researchers attributed the higher infection rate posed by mixed feeding to greater exposure to allergens, causing inflammation and damage to gut mucosal barriers, and to HIV, which in turn led to a higher infection rate. [60]

The negative impact of mixed feeding is further substantiated in research conducted in Zimbabwe as part of the Zvitambo study wherein over 14100 mothers were enrolled at the time of delivery and had an overall postnatal HIV transmission rate of 12.1%. The researchers found that, when compared to exclusive breastfeeding, mixed feeding resulted in a fourfold (4.03, 95% CI: 0.98;16.61) greater risk of HIV transmission after six months. By 12 months this risk was 2.60 (95% CI: 1.21-5.55) and by 18 months it was 2.63 (95% CI: 0.59-11.67).[61]

### 2.1.12. Summary

The data presented above on HIV and infant feeding indicate that even where technical guidance on the implications of safe infant feeding in the HIV context is provided, for an individual mother her personal household and family dynamics

are ultimately the most significant determinants of how she feeds her baby. There are however few studies that specifically document over time the impact of psychosocial factors on infant feeding choices and practices of mothers.

## 2.2. NUTRITIONAL STATUS AND HIV INFECTION AMONG WOMEN

### 2.2.1. Interactions between Nutrition and HIV infection

"Nutritional health is maintained by a state of equilibrium in which nutrient intake and requirements balance".[62] Once this equilibrium is upset, with nutrient intake being less than nutrient requirements, the result is malnutrition. Although not all HIV-infected persons are significantly malnourished or display severe wasting, the development of malnutrition may lead to clinical immuno-compromise and resultant HIV disease progression.[6]

Malnutrition is a common manifestation among persons living with HIV and AIDS and its causes are multi-factorial. On account of this, the effective management of the HIV-infected individual requires a multifaceted approach.[63] The malnutrition-infection cycle has been thoroughly explored[64] to explain the mechanism by which nutrition influences infection and the factors wherein infections lead to growth failure and clinical malnutrition. Others refer to the relationship between nutritional status and the course of HIV disease as "bi-directional" with HIV infection leading to wasting and progressive loss of both fat and lean body mass and, at the same time, wasting among HIV-infected people can be considered an independent risk factor in disease progression. [65]

The relationship between HIV infection, nutritional status and immune function has also been referred to as a "triad", whose main outcome, until the advent of antiretroviral drugs, was wasting.[66] It is known that inadequate dietary intake

can lead to loss of weight, wasting and low stores of essential nutrients. This situation is associated with a lowered immune system and poor ability to fight off any infections, leading to accelerated disease progression and severity.[67]

Optimal intake of micronutrients is likely to be affected by anorexia or difficult and painful swallowing during HIV infection. Decreased food intake, together with insufficient consumption of micronutrients has also been noted among asymptomatic HIV-infected adults, resulting in a significant loss of weight along with reported increased gut permeability in about 25% of such persons.[68, 69] There is documentation that HIV-infected persons do not consume the required levels of essential micronutrients.[70-73,74,75]

### 2.2.2. Body composition and HIV infection

The first formal assessment of body composition using high precision techniques among HIV-infected and AIDS patients was published in 1985 on the basis of mounting evidence of both visceral and somatic protein depletion.[75] However, it has also been stated that "despite the many women of reproductive age who are HIV positive, few studies have investigated the relationship between HIV infection during pregnancy or lactation with a focus on maternal nutritional status and health".[76] The wasting associated with HIV occurs as intermittent episodes of weight loss, lasting weeks or months and is often associated with acute opportunistic infections.[66]

The association between HIV-related wasting and opportunistic infections, such as tuberculosis, was demonstrated in a study conducted among HIV-infected persons in Malawi.[77] In this study of 579 HIV-positive women and men with sputum-positive pulmonary tuberculosis, severe wasting was common with 59% having a BMI of less than 18.5 kg/m², 32% of the subjects had a BMI less than

17.0 kg/m², and 17% of all the subjects were severely wasted as defined by a BMI of less than 16. Kg/m². In addition to wasting, most of the study participants were deficient in vitamin A, zinc and selenium.

*2.2.2.1. Prenatal and postnatal body composition trends among HIV-infected women*

It is known that HIV infection can have an effect on body composition from pregnancy through to the postnatal period. There are researchers that had previously disputed the fact that the postpartum changes in body composition were related to the energy demands of lactation, rather they concluded that weight loss observed among postpartum mothers was independent of the length of breastfeeding and an overall negative energy balance. Furthermore, these authors mention that the weight loss amongst these women could have been attributable to metabolic, hormonal or deliberate food deprivation. [78]

Additional data [79] indicate that the hydration and density of fat free mass does not return to pre-pregnancy values by two weeks and that it differs between lactating and non-lactating women. A study undertaken among healthy, HIV-free women in the United States used more sophisticated methods of determining body composition, namely total body water, underwater weighing, skinfold thickness, total body potassium, dual energy X-ray absorptiometry and total body electrical conductivity, with these measurements repeated till 12 months postpartum. The weight measurements in this cohort were 64.6kg at three months, 63.4 Kg at six months and 62.4kg at 12 months postpartum. They found that 10% of the women at each postpartum interval either gained weight or remained weight stable. They concluded that by three months postpartum the relative composition of fat free mass had returned to within the normal range between both lactating and non-lactating women. This study cannot be extrapolated to HIV-infected women in a developing country context as they are more likely to be nutritionally vulnerable than their US counterparts. However,

there is now a growing evidence base from Africa on the body composition changes among HIV-infected pregnant women and also postpartum women.

In Zimbabwe-based research[80] it emerged that, independent of CD4 counts, weight loss is a common manifestation of human immunodeficiency virus infection and that it is strongly correlated with predicting survival. In this study it was found that among 526 HIV-positive pregnant women and 1113 pregnant HIV-negative women, neither HIV infection (95% CI: -1.44;0.35, p=0.23) nor malaria (95% CI: -3.93;8.35, p=0.48) was a predictor of weight when gestational age, age, gravidity and season were controlled for in multiple regression analysis. However, women with viral load greater than 5log10 had 2.5kg (95% CI: -0.1;5.1) lower mean body weight than uninfected women if elevated serum ACT (alpha1-antichymotrypsin - an acute phase protein) was not controlled for. Elevated serum ACT was strongly inversely associated with weight as women with levels between 0.3 and 0.4, 0.4 and 0.5 and >0.5 g/L had almost 1, 2 and 6kg respectively lower mean body weight than women with levels <0.3g/l. Women with HIV infection had a 0.39cm lower arm circumference than uninfected women and they were also found to have 0.62cm lower triceps skinfold thickness than uninfected women, but this was also related to higher viral loads among the former. HIV status was found to be a predictor of arm fat area and all other anthropometric measurements and indicators declined with increasing viral load.

A study was conducted in Tanzania among HIV-infected women to investigate both the pattern and predictors of pregnancy weight gain.[65] This study found that those women who had a low CD4 count at baseline (12 weeks of gestation) had lower rates of weight gain in the second and third trimester compared to their counterparts with CD4+ counts of greater than or equal to 200cells/mm$^3$. They also found an average decrease in Mid Upper Arm Circumference (MUAC)

between weeks 12 and 38 of 1cm. It appeared that the women who at baseline had a MUAC greater than 29cm experienced the largest decrease in MUAC during pregnancy, overall 2.7cm. The decline in MUAC was influenced by other parameters such short maternal stature, conception during the rainy season and low selenium concentration.

To further investigate changes in body composition during the postpartum period, researchers set out to establish the effect of breastfeeding on the body composition of HIV-infected mothers. They found no significant differences in reported illnesses between the breastfeeding HIV-infected and breastfeeding non-infected mothers, with the exception of two women who had tuberculosis. In their group of mothers, at eight weeks, only 1.3% of the 92 HIV-infected mothers had low CD4 counts (i.e. <200cells/μL) and at 24 weeks only 3.3%. Median CD4+ cell counts at eight weeks and 24 weeks were 658 and 590 cells/μL respectively. As would be expected they found higher CRP levels (CRP>0.01g/L) in the HIV-positive mothers at 24 weeks (p=0.056). In terms of anthropometry, they found that none of the mothers at eight weeks could be classified as underweight or having a BMI <18.5kg/m2, but by 24 weeks two mothers (one HIV-positive mother and one HIV-negative mother) had a BMI <18kg/m$^2$. This may imply that with time there were some observable weight changes in the mothers. For MUAC measurement, at eight weeks postpartum, six mothers had MUAC measurements of less than 23cm (fifth percentile of US National Health and Nutrition Examination Survey) and at 24 weeks only three had low MUAC measures and one of these was HIV infected. They found that 26.4% of the HIV-infected mothers and 29.8% of the HIV-negative mothers were classified as mildly to moderately overweight with BMI of greater than 26kg/m2) at eight weeks. By 24 weeks the proportion of overweight HIV-infected mothers decreased slightly but increased in the HIV-negative mothers (22.9% vs 37.7% respectively; p=0.176). For general changes in weight it was found that

more HIV-infected mothers than those who were not infected lost weight between eight weeks and 24 weeks (70.0% vs 46.7% respectively; p=0.05). Overall, with time, the HIV-positive mothers lost weight whereas the HIV-negative mothers gained weight slightly (-1.4±3.1kg vs 0.4±3.3kg respectively, p=0.0004). These differences between the groups remained, regardless of baseline characteristics. There was also a noted non-significant weight loss amongst those mothers who had reported any illnesses during follow-up, compared to those who were never ill.[81]

In Tanzania it was found that HIV infection among pregnant women was a significant risk factor for wasting, especially if the women were of a low socio-economic status.[82] Studies on body composition and HIV vary, with some documenting the changes among asymptomatic HIV-infected persons whilst others focus on persons with more advanced HIV disease and compare them to HIV-negative persons. Research conducted to assess the trends in body composition within the African context was done in Rwanda[83]. Between 1992 and 1993 the study recruited both HIV-infected (n=101) and non-infected women (n=106) and followed them up for a period of nine months after delivery. Each woman provided an indication of their pre-pregnancy weight. They found that the weight (58.5kg) and BMI (24.1kg/m2) were lower among the HIV-infected pregnant women as compared to their HIV-negative counterparts (weight=59.3kg and BMI= 24.5kg/m2). The differences, when compared to the pre-pregnancy weight, between the two groups of women were larger at five months post-delivery, with the mean weight variation being -2.2kg (SD=5.9kg) in HIV-infected women and +0.2kg (SD=6.6kg) in the HIV-negative women and this difference was significant (p=0.007). This study found that during the post-delivery period significant differences in weight between HIV-infected (55.8kg) and non-infected women (58.7kg) were noted at three months; however, after nine months post-delivery the differences in weight between the two groups was non-significant. The authors concluded that the HIV-negative women tended to

recover their pregnancy weight by five months postpartum, whereas the HIV-positive mothers never regained their pre-pregnancy weight, yet in terms of disease progression none of them developed full blown AIDS.

Other researchers[84] studied the gender-specific changes in body composition that characterise AIDS wasting in women. They assessed body composition of three groups of women according to stage of wasting. The three stages were non-wasting defined as weight >90% ideal body weight, weight loss <10% of pre-illness body weight; early wasting defined as weight >90% ideal body weight, weight loss >10% of pre-illness weight; and late wasting as weight <90% of ideal weight. The CD4 counts of each of the groups were determined as well as lean, fat and muscle mass and BMI. The BMI for the non-wasted group was 24.4%, for the early wasting group 22.2 kg/m², and in the late wasting group 18.2 kg/m². The authors concluded that, unlike their male counterparts, women lose fat mass disproportionately to lean mass in the early and late stages of AIDS wasting. The explanation for this loss of fat mass could be related to an androgen deficiency, which was found to be common among women with AIDS-related wasting. However, there is a need for caution in extrapolating the findings of this research as its participants were at a more advanced stage of HIV disease.

The role of hormonal changes among HIV-infected women has been reported in the literature. HIV-infected underweight women preferentially lose fat mass and tend to preserve body cell mass, even in advancing HIV disease state determined by HIV RNA levels CD4 lymphocyte counts.[85] The authors propose that women tend to lose more fat mass possibly due to growth-hormone resistance. Additional data on the gender difference in either fat or lean body mass loss among HIV-infected women and men have been reported.[86] Using bio-electrical impedence analysis, researchers found that among men, fat free mass accounted for 51% of the weight whereas in women this was only 18% and these

differences were noted across African (Zairian) and American race groups. These researchers attribute the sex-related differences in body composition to hormonal "disease-induced hypogonadism" differences between males and females that begin from puberty onwards. From this stage girls tend to gain more fat and boys gain more body cell mass and skeletal muscle mass. The authors concluded that more data on the specific sex hormones that influence these body composition changes in HIV infection are required. It would appear that among men with HIV, wasting is characterised by loss of lean body mass, and sparing of fat stores. Others contend that it may be dependent on the predominant stores, either lean or fat in an individual i.e. that determines what component is lost at higher levels.[87]

In the USA several studies have been conducted on body composition changes primarily using bio-electrical impendence amongst men and women. These studies included complex analyses of body composition in that they were able to determine the fat free mass changes and percent body fat changes. According to one study, any weight loss seen among HIV-infected women was predominantly body fat, a high degree of individual variability in their data, and loss of fat mass among their study participants depended upon whether one had greater levels of body fat versus fat free mass initially.[87] However, they conclude that more studies are required to examine the relation of the initial body fat percentage and the subsequent loss of fat free mass in women with HIV and that these studies should include women who start off with a low initial percentage of body fat. Such data will assist in formulation of diets that assist in preservation of lean mass in HIV disease.

There is concern over the impact of infant feeding choices on maternal health and HIV disease progression because HIV-positive mothers who choose to breastfeed may be predisposed to greater body composition changes due to possible inadequate dietary intake as well and the increased nutrient

requirements and demands that are posed by breastfeeding itself as well as the HIV disease state.

Studies referred to earlier from Nairobi and South Africa[23,50] have provided differing evidence on the impact of infant feeding choices on HIV disease progression among women. However, neither of these studies at the time led to any global policy changes or recommendations on infant feeding in the context of HIV and AIDS. A more recent study from Nairobi that assessed HIV disease progression among breastfeeding and formula-feeding mothers found a significant decrease in BMI among current breastfeeders (-0.065) not formula-feeders (-0.027). This could be due to the caloric costs of lactation and the required increased energy requirements and weight loss.[5]

One of the challenges in assessing body composition trends among postpartum women is that it takes time for the pregnancy related over-hydration to return to pre-pregnancy levels. Researchers have mentioned that body composition measurements taken after pregnancy are more accurate when taken at least four to six weeks after delivery, due to the fact that hydration and density of fat free mass (FFM) do not return to pre-pregnancy values before this time.[8] Other authors state that it is only at three months postpartum that the relative composition of fat free mass returns to within the normal range, between both lactating and non-lactating women.[79]

A team of researchers in KwaZulu-Natal, South Africa[19], compared two methods of determining body composition changes among HIV-infected women, namely bio-impedence spectroscopy (BIS) and anthropometry with isotope dilution using doubly-labelled water to measure fat free mass (FFM) and fat mass (FM) in both HIV-infected and uninfected breastfeeding mothers. According to the authors, HIV-infected breastfeeding mothers, 95% of whom had >200 cells/μL CD4 counts on average lost weight between eight and 24 weeks postpartum, whereas

their HIV-negative counterparts gained weight, but remained within the normal cut-off points of BMI. The loss in weight among the HIV-infected mothers was due to a loss of fat mass, as the HIV-infected mothers had less subcutaneous fat. The greatest predictor of weight loss among the HIV-infected mothers was reported illnesses, whereas for HIV-negative mothers the predictor was the initial levels of weight. They found little evidence of the typical HIV wasting in this group of women because most women remained within normal BMI ranges, but it was also noted that the mean percentage body fat in all mothers at 24 weeks in this study (32%) was considered to be generally higher than that of lactating women elsewhere.

*2.2.2.2. Body composition trends, survival and initiation of HAART*

Prior to the global initiation of highly active antiretroviral therapy (HAART), HIV-related wasting was regarded as one of the main manifestations of disease progression. However, with the introduction of HAART there has been an observation of "HIV-associated adipose redistribution syndrome (HARS)". HARS results in subcutaneous fat distribution and abdominal obesity which are related to disorders of the metabolic system.[88] It has been stated that that whilst the severe wasting and malnutrition that characterised the earlier depiction of HIV and AIDS has diminished given the anti-retroviral (ARV) therapies available, it has not totally disappeared as some patients either choose not to take combination therapies or some are now treatment resistant.[75] This statement is further corroborated by data from a cohort study among HIV patients[89] in the USA which found that even with the availability of HAART there is a risk of $\geq$ 5% increase in unintentional weight loss over six-month periods, even though the participants had better control over their HIV disease state and opportunistic infections.

The effect of HAART on body composition has been studied by researchers [90,91,92] in varying settings resulting in different outcomes reported on whether lean body mass increases or decreases when HAART is provided. The body composition changes are likely to be influenced by the particular drug regimen used whether it is mainly the protease inhibitors or nucleoside reverse-transcriptase inhibitors (NRTI) and non-NRTI (NNRTI). A lower CD4+ cell count at baseline predicted a greater loss of trunk and limb fat and it was found that lipo-atrophy that is observed is the unique physical manifestation of HIV infection, but it was not possible in this study to separate out the individual effects of anti-retroviral therapy as they are often used in combination. Investigators reported that they are unable to attribute the loss in weight to decreased energy intake, malabsorption, increase physical activity or energy expenditure associated with the HIV disease state or other illnesses or a combination of all these factors.[90]

Data from several studies have indicated that the length of survival in persons living with HIV and AIDS and their nutritional status are related. However, it is still important to establish whether nutritional status is an independent predictor of survival in infected HIV-infected women.[90,92]

To analyse the relationship between nutritional status and disease progression a US study stratified HIV-infected persons by the levels of CD4 counts. They also scored age at either<35 or ≥35 because this classification had been shown to have prognostic significance for survival of HIV patients in previous research. The majority of subjects in this study were men. This study highlighted that there is a lot of individual variability as some people with low CD4 counts can remain of normal weight whereas others may become severely malnourished.[92] Thus, weight loss alone might not be a strong predictor of survival among HIV-infected persons; instead, it is important to ascertain the percentages of body cell mass or fat free mass as well. They found that their study agreed with

previous research that indicated that HIV-infected individuals who are older, have lower CD4 counts or have more advanced malnutrition have decreased lengths of survival. However their research was in males and it is uncertain if the same conclusion about women's age could be reached in a similar study involving younger women.

#### *2.2.2.3. Summary*

From the data it is apparent that HIV disease influences body composition changes starting in pregnancy and during lactation. Additional data is drawn from infected women and men primarily in the USA where more invasive methods of assessing body composition were used. There appears to be a preferential loss of fat mass over lean body mass in women and some researchers have associated this with hormonal levels and others have postulated that this could be related to the initial levels of fat mass that the women had before HIV disease.

### 2.2.3. Maternal micronutrient status and HIV infection

There is now a growing research base within the developing world, and primarily from Africa, on the role of micronutrient deficiencies in mother-to-child transmission of HIV and in HIV disease progression.[93,94,95] Micronutrient deficiencies, even in the absence of HIV infection, have been documented to affect global health outcomes, incurring substantial economic costs. With specific reference to women and female adolescents and children, the socio-economic costs associated with these deficiencies are considerable, though not always well quantified.[96] For a full assessment of the impact of micronutrient deficiencies on maternal health there should be consideration of the functional and health

outcomes, mental aspects, immuno-competence, physical work capacity, morbidity and mortality.

### *2.2.3.1. Mechanisms by which HIV infection impacts on blood micronutrient levels*

In 2003, the WHO established a Technical Advisory Group (TAG) on Nutrition and HIV/AIDS comprised of international experts in nutrition and HIV/AIDS research, policies and programmes. One of the mandates for the TAG was to review the current evidence and science on the role of micronutrients in HIV disease.[97] The literature review below will prioritise the impact of micronutrient deficiencies among HIV-infected women.

By the late 1980's and 1990's there was still a dearth of research documenting the estimated effects of micronutrient deficiencies on infectious disease morbidity and mortality. Human immuno-deficiency virus is an infection which has been documented to impact negatively on the nutritional status of the infected person. The malnutrition-infection cycle acknowledges that this impact is two-fold and cyclical, with infections such as HIV leading to reduced food intake, lowered absorptive capacity of essential nutrients and it may also increase the levels of nutrient requirements.[98] Figure 1 has been developed to illustrate the relationship between micronutrient deficiencies and HIV disease progression.

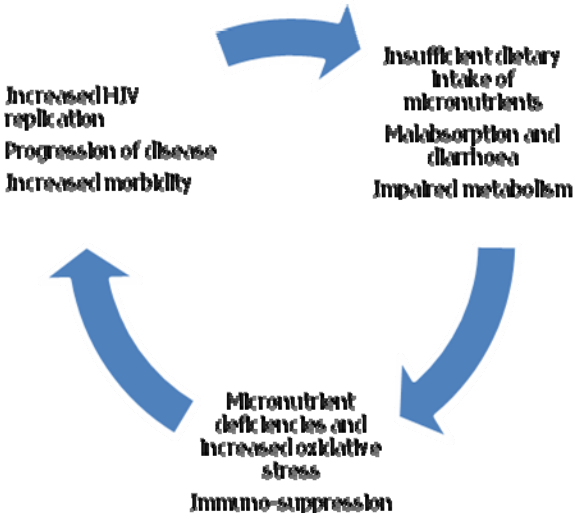


**Figure 1:** Vicious cycle of micronutrient deficiencies and HIV pathogenesis [98]

The full impact of micronutrient deficiencies is dependent on the nutritional status of the infected person prior to infection. One review[99] describes the impaired immune functions resulting from lack of micronutrients as "nutritionally acquired immune deficiency syndrome" or NAIDS. NAIDS "contributes to the depletion and dysfunction of CD4+ cells and make the host susceptible to other infections which may increase viral replication, thus accelerating HIV disease progression". Other authors[100] state that NAIDS is the most prevalent immuno-suppressive disorder globally. The literature acknowledges that deficiencies of micronutrients begin in early HIV infection and, in particular, there is growing evidence of deficiencies among HIV-infected pregnant women, who by virtue of their pregnancy are likely to have increased micronutrient requirements. It has been shown[93,98,101] that a malnourished person has greater susceptibility to HIV-related infections and thus a worse prognosis. However, it is difficult to demonstrate that specific nutritional deficiencies contribute to poor clinical outcomes in the presence of HIV.

It is known that micronutrient deficiencies may lead to nutritionally-related immuno-suppression and oxidative stress, which results in accelerated HIV disease progression.[98] The exact mechanism by which infections such as HIV impact on nutrition is "mediated by the acute phase response which is a stereotypic host response to infection, inflammation and accidental trauma due to the release of pro-inflammatory cytokines from activated macrophages"[102]. Thus any assessment of the role of micronutrients in HIV disease needs to factor in the acute-phase response. This acute-phase response is attributable in part to the free radical theory. It is believed that micronutrient deficiencies can precipitate oxidative stress, a condition that results from an imbalance between pro-oxidants and antioxidants, resulting in overproduction of reactive oxygen intermediates (ROI). The ROI produced can themselves induce cellular injury and lysis because the free radicals can cause "oxidation of nucleic acids, chromosomal breaks, peroxidation of lipids in cell membranes and damage to collagen, proteins and enzymes."[98,103]

Specifically in relating HIV infection to micronutrients, it has been found that HIV infection itself increases oxidative stress leading to oxidative damage, and the extent of this depends on the body's own antioxidant enzymes to whose activity select micronutrients such as vitamin A, E, and selenium contribute.[104]

Researchers have emphasised that any assessment of the role of micronutrients in HIV disease state and progression needs to factor in the acute-phase response, as there is evidence of a nutritional cost of the acute-phase (or inflammatory) response.[102] In severe infection the acute-phase response may result in infection-induced malnutrition, due to increased nutrient requirements and also decreased food intake and absorptive capacity. Other authors[105] mention that in recent years there has been growing interest to study host inflammatory response to infections. They explain that "during infection, cytokines are released by the activated cells, thus generating and maintaining

innate and specific immunological responses," one of which results in the production of acute-phase proteins such as C-reactive protein or CRP. In the literature, researchers either use CRP or alpha acid glycoprotein, or alpha-antichymotrypsin or ferritin to measure the acute phase response. [101,106].

### *2.2.3.2. The role of vitamins and minerals on pregnancy outcome and MTCT of HIV*

Maternal macro- and micro-nutrient status during pregnancy is an important predictor of birth weight and intrauterine growth retardation, even in the absence of HIV infection.[107, 108,109,]

Data from Africa documents the role of HIV-disease state and of maternal nutritional status before and during pregnancy in predicting pregnancy outcomes and vertical transmission of HIV. Research was conducted in Tanzania to assess the socio-demographic, nutritional and infant risk factors for low birth weight and small-for-gestational-age status among a cohort of 822 HIV-positive women who were part of a clinical trial of vitamin A supplementation and pregnancy outcomes in Tanzania. Women with very low serum retinol concentrations (<0.35µmol/L) delivered infants with significantly lower birth weight than those women with higher serum retinol concentrations (≥ 0.70µmol/L). In addition, it was found that HIV-disease progression impacted negatively on low birth weight incidence in this study, with infant birth weight being significantly lower in women in stage III HIV state than in women in stage I (-463g; 95% CI: -821, -105g). Findings from this study lead to the conclusion that immuno-suppression in HIV-positive women may contribute to low birth weight by increasing women's susceptibility to infection and by compromising their nutritional status, however the mechanism by which this occurs has not yet been established.[109]

Additional data from Tanzania[65] showed that not only did weight gain among HIV-infected pregnant women decrease during a 15-week observation period, but significant risk factors for low rates of weight gain during pregnancy included having a low education level, reduced financial expenditure on food, short stature, low serum retinol (<0.35µmol/L) or selenium concentrations and advanced HIV-disease state.

Whilst maternal vitamin A deficiency has been associated with a higher risk of MTCT of HIV, the relationship is not a causal one as plasma vitamin A concentrations may be poorly associated with plasma HIV load.[103] One observational study suggested that low serum retinol increases the risk of mother-to-child transmission of HIV[110] but this was not confirmed by other trials of vitamin A and beta-carotene supplementation.[111] Data from Malawi[107], where HIV-infected pregnant women were supplemented with 10,000IU vitamin A pre-natally or received a placebo, did not show any effect of the vitamin on HIV transmission at six weeks or 12 months, but resulted in an improvement in birth weight. A study from South Africa similar to the Malawi study showed a significant reduction in the rate of premature births but no effect on birth weight.[113]

Selenium deficiency has been cited as a risk factor in mother-to-child transmission of HIV through all three possible routes of transmission, namely in pregnancy, at delivery and through breastfeeding.[113] In a study conducted among HIV-infected women in Tanzania, in which plasma levels of selenium were measured and CD4 counts were determined, levels of selenium were found to be proxy indicators for levels of other micronutrients among the women. In particular, high selenium levels were found to be marginally associated with higher vitamin A levels and lower vitamin E and haemoglobin levels. The HIV transmission risk in this study was found to be 34%. In particular, the study found the blood levels of selenium were inversely associated with the risk of

transmission during delivery and the early breastfeeding period (p=0.01). There was no association between low selenium levels and preterm or low birth weight deliveries; however, those children born to women with low levels of selenium were at increased risk of foetal death and child deaths within the first two years of life.

### *2.2.3.3. Micronutrient deficiencies and HIV disease progression*

In reviewing the literature, it emerged that some of the initial data relating micronutrient status to HIV-disease progression were primarily undertaken in the developed world, mostly in the USA among homosexual males and drug users.[114,115,116] However, from the early 2000's the data began to evolve on the specific role of specific micronutrient deficiencies among HIV-infected women, starting in adolescence[117] and into pregnancy[118,93,101] In addition, there are now several reviews that have documented the role of vitamins and minerals in HIV.[100,102,119,120,121] There is inconsistent evidence that nutrition interventions improve nutrition outcomes. However, it is true that impaired nutritional status is associated with worse outcomes, but this can probably be attributed to an HIV effect which may or may not respond to nutritional interventions.

It has also been documented[122] that nutrient deficiencies tend to be highly prevalent in asymptomatic HIV-1 infected individuals and, in particular, zinc, along with vitamins A, E, B6 and B12 have each been found to play a role in optimal immune function. In research undertaken among 125 HIV-infected female drug users, who were examined every six months for a total of 3.5 years with blood parameters of nutritional status and immune function being collected at the same time, it was found that, with advanced HIV-1 disease, nutritional alterations were particularly marked by significantly lower plasma levels of vitamins A and E, selenium, retinol-binding protein and pre-albumin in

comparison to their male counterparts. The authors of this study furthermore mention that although nutritional factors are unlikely to be the most important aetiological determinants of HIV disease, they influence the initial susceptibility and subsequent disease progression.

Evidence from Zimbabwe[101] indicates that vitamin A, beta-carotene and folate and several other micronutrients are lowered in HIV-infected pregnant women. Vitamin A deficiency among women during pregnancy and lactation is known to have adverse effects of morbidity and mortality on both the mother and the infant. Among well-nourished mothers there is sufficient (>2µmol/L) vitamin A in the breast milk to benefit the newborn breastfed infant.

An intervention study on the effects of multiple micronutrient and vitamin A supplementation was undertaken in Tanzania[123]. In this study, 1078 pregnant women infected with HIV were enrolled in a double-blind placebo controlled trial in Dar es Salaam, Tanzania. The study was conducted to examine the effects of daily supplements of vitamin A, multivitamins (B, C, E) or both on disease progression using survival models. The follow-up period in the study was 71 months. Of the 1078 women, 299 progressed to stage 4 (or AIDS) or died. Of the women who died, 24.7% were on multivitamins, 26.1% were on multivitamins and vitamin A, 29% were on vitamin A alone and 31.1% received placebo. The authors concluded that as compared to placebo, women who received multivitamins were less likely to progress to stage 4.

A concern that arose from the findings of this study was that vitamin A supplements given alone had no significant effects on improving CD4 counts or reducing viral load. Furthermore, this study found that adding vitamin A to the multivitamin supplement reduced the overall benefit of multivitamins alone. However, the global recommendations from WHO, UNICEF and the International Vitamin A Consultative Group, 1997[124] remain that in areas where vitamin A

deficiency is endemic, women should receive a single dose of vitamin A (200,000IU) as soon as possible after delivery and not later than six to eight weeks post-delivery. The United Nations (UN) also recommends that in communities where there are multiple micronutrient deficiencies, appropriate supplements should be provided for pregnant and lactating women that cater for all the deficiencies.

Selenium has been documented as one of the minerals that may delay HIV-disease progression. This function arises from the roles of selenium as an antioxidant, in thyroid hormone metabolism and in reproduction and immune function.[125] There has been expansion on the role of selenium in regulating the activity of the antioxidant enzyme glutathione peroxidase. Low blood levels of selenium in HIV disease have been associated with low glutathione peroxidase activity, but with selenium supplementation it has been possible to reverse this trend.[105] There is evidence from Tanzanian HIV-infected pregnant women indicating that those followed-up over a 5.7 year period and who had low blood levels of selenium had significantly increased mortality ($p=0.01$).[126]

An exploration of the role of micronutrient supplements in HIV disease is obtained from studies assessing the effect of dietary intake of micronutrients, whilst others document the effect of micronutrient supplements (either as a single nutrient or a combination of nutrients) on HIV disease progression among adult men and women. The micronutrient supplementation studies can be categorised broadly into either longitudinal observational studies or observational and randomised placebo controlled studies. Thus, given the differences in methodological approach of the studies, the formulation and dosage of micronutrients offered in the supplement, the findings can at times be contradictory. For instance, a randomised controlled trial evaluating the effects of multivitamin supplements on HIV-disease progression in Tanzania found that inclusion of vitamin A as one of the arms of the trial resulted in lower CD8+ and

CD3+ cell counts, whereas multivitamin supplementation with the B-complex vitamins, vitamins C and E significantly slowed disease progression, thus raising concern that vitamin A supplements may produce adverse outcomes in HIV-infected populations.[123]

On the other hand, earlier studies on vitamin A deficiency and disease progression[127] among HIV-infected male drug users found low vitamin A levels led to faster HIV - disease progression. Yet, among HIV-infected, vitamin A-replete males in the USA[128], there was a less clear association between lower levels of serum vitamin A and HIV-disease progression. This latter population, however, was taking vitamin A supplementation. But among HIV-infected lactating women in South Africa it was found that, on average, retinol was significantly lower in HIV-positive mothers, even after controlling for the acute phase response.[129]

In a randomised placebo controlled trial in Zimbabwe to assess whether a single high-dose vitamin A supplement (400,000IU) can reduce the HIV incidence among postpartum women, it was found that the supplement had no effect on the HIV incidence (Hazard ratio [HR]: 1.08; 95% CI: 0.85-1.38]. However, the high-dose supplement did have a protective effect if the women were found to have low serum vitamin A levels (<0.7µmol/L) prior to commencement of the trial.[130]

Regarding serum vitamin B12[68] and vitamin E[128] there is documentation that deficiencies of both these vitamins can lead to faster HIV disease progression among adult males in the USA. In a study conducted among HIV-infected lactating women in South Africa[7], who were followed-up until 24 weeks after delivery, it was found that less than 45% of the mothers had sufficient serum levels of either vitamin B12 or folate. Significantly more HIV-positive (70.5%) than HIV-negative (46.2%) mothers had marginal vitamin B12 status ($p< 0.05$).

At 24 weeks, 70% of the infected and non-infected mothers had an alpha-tocopherol deficiency (< 11.6 micromol/L), but the difference was not significant.

In a review of a large retrospective observational database of HIV-infected patients in a Johannesburg Hospital, prior to the introduction of ARV therapy, it was established from a classification tree analysis (CTA) model that those African patients who received therapeutic doses of multivitamins, B complex vitamins or pyridoxine had delayed HIV disease progression. The median time to HIV disease progression was 32 weeks for those persons not on any vitamin supplementation, whilst for those patients who received supplementation the time to disease progression was 72.7 weeks. The differences between the groups getting vitamin supplements and those not getting them were significant for both median duration to AIDS (p=0.004) and median survival time (p=0.001).[131] It is possible, however, that the marked impact of vitamin supplementation may also be reflective of prior vitamin deficiencies in the group of persons being studied.

One of the fundamental flaws in micronutrient supplementation trials is the assumption that, for the population under review, everyone is deficient in the micronutrient being supplemented and therefore the intervention will have a positive effect on this.[120] Some of the trials, including both observational and randomised placebo controlled trials, which have been conducted in the past, focused on supplementation with a single nutrient. Yet, it must be realised that most nutrients interact with each other and therefore any supplementation trial should focus on a multiple micronutrient approach. In a review of the supplementation trials in women and children with HIV infection, which compared vitamin A, and ß-, carotene supplements with placebos, none showed a demonstrable effect on mortality, morbidity, CD4 and CD8 counts or on viral load.[132]

Studies previously undertaken among homosexual males and drug users concluded that HIV-infected men and women with nutritional deficiencies have a high risk of mortality. It was also established that sub-clinical malnutrition measured by serum albumin concentration and levels of vitamin A, B12 and selenium deficiency over time were each associated with HIV-related mortality, independent of CD4+ lymphocyte count <200cells/mm³ at baseline and over time. In addition, only selenium deficiency was associated with decreased HIV-disease survival and this effect remained when controlling for overall deterioration of nutritional status and baseline and over-time CD4 counts.[133]

Other research teams[102] mention that iron deficiency is the most common cause of low haemoglobin concentration, but vitamin A, riboflavin, vitamin B-12, folate and zinc are also important to erythropoiesis. Investigations have been conducted to determine the effects of zinc supplements on birth outcomes, haematologic indicators and counts of T-lymphocyte subsets among 400 HIV-infected pregnant women in Tanzania[134]. They found no beneficial effects of zinc supplements on pregnancy outcomes and instead found that zinc supplementation has a negative effect on haemoglobin concentration, which was used as a proxy indicator of HIV disease stage. Whilst both the group of women who received zinc supplements and the placebo group experienced an increase in haemoglobin concentration between baseline and six weeks postpartum, the increase was lower in the zinc supplemented group (11.5$\pm$ 17.9g/L) vs (15.2$\pm$18.6g/L). It has been proposed that increased levels serum zinc are likely to have a negative effect on iron absorption.

High serum levels of iron or zinc have been found to contribute to accelerated HIV disease progression.[135] Iron has been shown to accumulate in several tissues in the body during HIV infection and the levels increase with more advanced disease progression.[136] The accumulation of iron is attributable to the chronic

inflammatory response that results in increased storage of iron away from the circulatory system. There is also evidence that the accumulation of iron among HIV-infected persons may lead to the development of opportunistic infections and general weakening of the immune system. On account of this there are some researchers that believe that iron intake should be restricted among HIV-infected persons. Yet in a randomised placebo controlled double blind trial of iron supplementation (60mg elemental iron, twice weekly for four months) among HIV-infected persons in Kenya, HIV viral load did not increase[137]. The authors suggest that this may be because the levels of iron in the supplement were lower than those usually distributed in routine supplementation programmes.

To assess the impact of B-vitamins on HIV disease progression, researchers[114] examined the association between serum concentrations of vitamins B6, vitamin B12 and folate and the risk of progression to first acquired immuno-deficiency syndrome (AIDS) diagnosis and CD4+ cell decline over a nine-year period. Findings were that participants with low serum vitamin B12 concentrations (<120pmol/L) had significantly shorter AIDS-free time than those with adequate B12 concentrations (median AIDS-free time). Additional findings were that low vitamin B12 concentrations preceded disease progression. On the other hand, low serum concentration of vitamin B6 and folate were not associated with either progression to AIDS or decline in CD4 and lymphocyte count.

*2.2.3.4. Dietary micronutrient intake, blood micronutrient levels and HIV disease*

There are also studies that have assessed the dietary intake of persons living with HIV in order to determine adequacy of intake relative to the recommended dietary intake. One such study[114] assessed dietary intake of the study population and correlated the findings with serum levels of micronutrients. Mean and medium intakes from food and supplements combined were found to be above

the Recommended Dietary Allowances (RDA) for all three micronutrients studied. The same was not, however, the case among HIV-infected South Africans, whose micronutrient intakes were lower than the RDA levels.[74,138]

Other data relating dietary intake of micronutrients to biomarkers of nutritional status and disease progression amongst homosexual/bisexual males was obtained in the United States.[18] The highest levels of total dietary intake from food and supplements of vitamins C and B and niacin were associated with a significantly decreased progression to AIDS. They also noticed adverse effects of a high or low intake of vitamin A on disease progression. In a final multi-nutrient model they found only vitamin A, niacin and zinc deficiencies and low dietary intakes were significantly associated with progression to AIDS. Within the African context, vitamins and mineral supplements may not be as easily accessible or affordable as in the USA, thus fewer HIV-infected persons will be taking such supplements.

One of the earlier studies to understand the relationship between nutritional status, including micronutrients, and HIV infection in South Africa was undertaken in the Free State Province[74]. The impact on nutrition was assessed through laboratory parameters. In this study they recruited 90 HIV-1 sero-positive patients (male and female) from the immunology clinic between January and May 1995 and obtained blood samples to determine nutrient levels. Whilst the follow-up period among these patients was short, with only 16 patients followed-up in 1997, the researchers nonetheless found abnormal levels for several biochemical and haematological parameters among the HIV-infected persons as compared to the standard laboratory reference values.

Patients enrolled were deficient mainly in the antioxidant nutrients, namely albumin, vitamin C, vitamin E and retinol. About 60% of the patients had a significant decrease in haemoglobin levels, 55.5% had low serum ferritin, and

also low levels of vitamin B12 and serum folate. The study participants in this study were divided into 3 groups according to their CD4 counts, namely group 1: ≥ 500 cells/mm³, group 2: 200-499cells/mm³ and group 3: <200 cells/mm³. The majority of the patients had TB co-infection (30%), syphilis (10%), pneumonia (4.4%), dermatologic complaints (11.1%) and candidiasis (6.6%) and 15.5% were completely asymptomatic. Significant differences were noted for serum albumin (group 3 having significantly lower levels than group 2 (95% CI: -10;-1), serum ferritin (values for group 3 (95%CI: 3;128) and group 2 (95% CI: 10;158) significantly higher than for group 1. For vitamin E, there were significantly lower levels in group 2 than in group 1. The authors acknowledge that the differences in serum levels may be due to an acute phase response to HIV co-infections rather than a direct reflection of a deficiency. This study also attempted to correlate dietary intake of specific nutrients, anthropometry and biomarkers in a sub-group of 35 patients, however, given the small sample size it was not possible to observe any meaningful relationships.

Another study in the North West Province of South Africa compared nutrient intakes (using a validated quantitative food frequency questionnaire and biomarkers of nutritional status among 216 asymptomatic HIV-infected men and women and controls).[139] No statistically significant differences in mean nutrient intakes among the HIV-infected and non-infected study participants were found. However, the micronutrient intakes were sub-optimal. Furthermore, this study found that total body fat percentages also did not differ significantly between HIV-infected and non-infected subjects.

More recent data also from the Free State Province in South Africa[138] indicates that amongst HIV-infected women aged between 25 to 44 years, between 46.6% and 70.7% consumed ≤67% of the RDA for the essential minerals and vitamins namely total iron, selenium, folate and vitamin C. In addition, a quarter of the women in this study consumed sub-optimal levels of vitamins A, D and E.

The authors recommend that, on the basis of their study findings, HIV-infected women should be supplemented with essential vitamins and minerals.

*2.2.3.5. Micronutrient levels and initiation of HAART*

There is some data indicating that ARV therapy may alter the host response to some micronutrient biomarkers, by either increasing or decreasing the levels. Researchers investigated the effect of HAART on micronutrient levels among men and women in the USA.[140] This study consisted of 171 men and 117 women recruited between 2000 and 2003, with 62-69% having undetectable viral loads, most were in their mid 40's and had been infected for an average of 10 years. Most of the study participants were classified as poor.

The researchers found that with the exception of zinc, micronutrient deficiencies were less common than amongst persons not on anti-retrovirals. None of the micronutrient levels significantly affected CD4 counts and viral loads tended to be lower in persons with higher zinc and selenium levels, though not statistically significant. None of the women were deficient in vitamin E (<500µg /dL), but 36% of the women were deficient in zinc (less than 670µg/L). Selenium deficiency (<85µg/L) was observed in 3% of the women, and a vitamin A deficiency prevalence of 14% was also observed. In women the lowest retinol levels were found in the women with the lowest viral loads and this was statistically significant ($p<0.05$).

In a review paper on the relationship between micronutrient levels and HAART, researchers confirmed that micronutrient supplements can be used as an adjunct to HAART, however in some cases it has been established that micronutrient levels may become replete after HAART initiation. Because of the contradictory evidence reviewed by these researchers they recommend the need for further

studies to assess whether micronutrient supplementation is both essential and beneficial when providing HAART or is more likely to have adverse effects.[141]

*2.2.3.6. Summary*

There is sufficient evidence to indicate that micronutrients are important in the optimal functioning of the immune system, however, due to complexities in studying the contribution of individual or combinations of micronutrients, it is not possible "to define the areas where micronutrients may help in maximising the clinical status of HIV-infected patients".[135]

The role of micronutrients in prevention of mother-to-child-transmission and in delaying disease progression is well documented both in developed countries and on the African continent. However data on the consistent benefits of micronutrient supplementation among persons living with HIV is more ambiguous. Some studies include an assessment of multiple deficiencies because seldom do single deficiencies of any micronutrient occur alone. There are, however, differences in the length of follow-up, especially in those studies that are relating either dietary micronutrient intakes and or serum micronutrient levels to disease progression. Some studies ensured that when measuring serum levels of micronutrients amongst HIV-infected persons there is an adjustment for the acute phase response and various studies have used different acute phase response proteins, like CRP or serum ferritin, whilst others used alpha-1 antichymotrypsin. Furthermore, there are intervention studies where micronutrients are provided as prenatal supplements to assess the impact on birth outcome or on mother-to-child-transmission of HIV-1. Others have pleaded for evaluation of the effects of micronutrients in larger populations, especially among persons who are at more advanced HIV-disease states.[142]

Among HIV-infected pregnant women, optimal levels of micronutrients may affect maternal weight gain and also may influence birth outcomes such as birth weight and neonatal survival. In a study including zinc supplementation to HIV-infected women it was found that the supplement resulted in decreased concentration of iron and red blood cell count and had no effect on CD4 counts. This negative impact (especially on haemoglobin concentration) of the zinc supplement led the researchers to recommend avoidance of prenatal supplements for HIV-infected women.[134]

In HIV-infected adults, low CD4 counts over time and deficiency in vitamin A, vitamin B12, zinc and selenium may result in increased mortality. In particular, selenium deficiency was the only independent predictor of survival after controlling for baseline CD4 counts and CD4 counts ≤200/mm³.[143]

As more eligible HIV-infected persons across the world access ARV therapy, researchers have also assessed the effect of treatment on micronutrient levels. Presently it would appear that there is a need for more evidence from randomised controlled trials to fully assess whether micronutrient levels are enhanced or depleted amongst persons receiving HAART, as the current evidence base is not yet conclusive.[106]

## 2.3. MATERNAL HEALTH, HIV AND GROWTH OF HIV-EXPOSED CHILDREN

### 2.3.1. Overview of maternal HIV infection and nutritional status on child outcomes

Maternal nutritional status during pregnancy is an important predictor of birth weight and intrauterine growth retardation independent of clinical HIV disease progression, as described earlier. It is acknowledged that maternal nutritional

status before and during pregnancy is an important predictor of poor pregnancy outcomes and studies are appearing in the literature to examine these relations in the presence of HIV infection. It is also known that HIV infection increases micro- and macronutrient requirements as part of the body's immune response. Thus women who are both pregnant and HIV-positive are likely to be at an additional health and nutrition risk. According to one author, the direct and indirect causes of maternal morbidity and mortality may be more severe or debilitating in HIV-positive women, especially those with symptomatic HIV disease or AIDS.[144]

It appears that infants who become HIV infected in utero, at birth or postnatally through unsafe infant feeding are at a high risk of poor growth, frequent infections and early death.[145] The poor growth patterns of the HIV-exposed infants may be apparent even if they themselves are not infected with HIV. Furthermore, it has been shown that when the caring ability of a parent infected with HIV is compromised, this has a direct bearing on optimal growth and development of their infants.[146]

### 2.3.2. Trends in child mortality and HIV prevalence

Within South Africa there have been significant reversals in the trends of national indicators on infant and child mortality since the advent of HIV and AIDS. According to the Medical Research Council (MRC) of South Africa, 13% (294,000) of all HIV infections in children are in South Africa.[147] The 2003 South African Demographic and Health Survey[57] shows a 3% under-five mortality reduction, from 60 per 1000 live births in 1990 to 58 per 1000 live births in 2003. However, other sources[147] cite much higher under-five mortality estimates of 95 per 1000 live births.

The 2003 Burden of Disease Study[147] identified the top twenty mortality causes for children under the age of 5 years, with HIV/AIDS as the leading cause of death among young children, accounting for 40% of the deaths in 2000. Diseases associated with poverty (diarrhoea, lower respiratory tract infections and malnutrition) account for 20% of all deaths, and neonatal causes (low birth weight, asphyxia and infections) are responsible for another 16.4% of all deaths. In addition, in high HIV-prevalence settings child mortality has been associated with maternal illness and death.[148]

Whilst South African trends on infant mortality and HIV status exist, the effect of the HIV/AIDS epidemic on infant and child mortality is not easily measurable as the survival of the children exposed to HIV depends on their own parents and caregivers' health and HIV status.[149] A study to estimate the effects of maternal HIV status and other factors on infant mortality was undertaken and it established that infants born to HIV-infected mothers were three times more likely to die during infancy as compared to those born to uninfected mothers (HR=3.01; 95% CI: 1.64,5.50). The study concluded that, in Ghana, maternal HIV infection was a strong predictor of infant mortality. In addition, this study established that one in every ten children in the survey was born to an underweight mother (having a BMI <18.5 kg/m2). There was also a significantly higher infant mortality rate among boys (71) than girls (56). Being born with low birth weight was of greater mortality risk than children born with a normal birth weight. This finding was established regardless of infant feeding practice. This study did not include any analysis of the infant HIV status in relation to maternal health.

### 2.3.3. Child growth, morbidity, mortality and HIV infection

A study conducted in Zambia set out to investigate the factors contributing to poor growth of infants born to HIV-infected mothers between 2001 and 2003.

This study was conducted within a community where the preferred choice of infant feeding for HIV-infected mothers is breastfeeding, primarily due to the very high cost of infant formula. During the 16-week follow-up period, infant growth was measured through weight and height determinations and maternal health was assessed, including breast health, and haemoglobin status was also assessed in the women.[150] The data presented in this study was on 85 of 211 infants (40%) due to loss-to-follow-up or early infant death of some of the infants. Nineteen percent (19%) of the infants born to HIV-infected mothers and 11% born to un-infected mothers were born prematurely before 37 weeks gestation. Of these preterm children, 31% had a birth weight (<2.5kg) whilst of the term babies there were 7% who were of low birth weight. Between the six and 16 weeks follow-up period it was found that infants of HIV-infected mothers tended to have a lower weight/age and length/age Z-score than infants born to non-HIV-infected mothers and this difference was statistically significant ($p=0.04$) for weight at 6 weeks. However, when the infant birth weight Z-score was included in the analysis the effect of maternal HIV status on weight at six weeks ceased to be significant ($p=0.13$). In terms of infant feeding practices this study found that infants who were exclusively breastfed between 6 and 12 weeks had consistently lower Z-scores compared with infants exclusively breastfed for less than six weeks or for at least 16 weeks.

The authors of this paper concluded that HIV-exposed, uninfected Zambian infants displayed poor growth from as early as 6 weeks postpartum, primarily due to low birth weight. This study therefore placed emphasis on optimal maternal health interventions as a child survival intervention. This study did not, however, assess maternal CD4+ counts and viral load and it was not possible to determine the role of maternal disease burden on growth trends of the children in this study.

An additional study from Zambia investigates the linkages between maternal HIV status and infant health[151]. In this study they followed-up a cohort of 620 HIV-infected infants born to HIV-infected mothers in order to investigate associations between markers of more advanced maternal HIV-disease, child mortality and hospital admissions and infant weight till 4 months of age. They found mortality among the uninfected infants to be 4.6% (95% CI: 2.8-6.3) till 4 months of age. Infants whose mothers had $CD4^+$ T-cell counts of <350 cells/μL were more likely to die (HR: 2.87; 95% CI: 1.03–8.03) and were more likely to be hospitalised (HR: 2.28; 95% CI: 1.17–4.45) after adjusting for other factors, including maternal death and low birth weight. They also found that a maternal viral load >100,000 copies/mL was associated with significantly lower child weight up till 4 months of age.

In order to calculate the excess risks of child mortality as a result of maternal HIV status data was pooled from three longitudinal community-based studies that classified births by maternal HIV status from Uganda, Tanzania and Malawi.[15] The excess risk of child deaths associated with having an HIV-infected mother is 2.9 (95% CI: 2.3-3.6) and this effect lasts throughout childhood. On the other hand, they found that the excess risk associated with a maternal death is 3.9 (CI: 2.8-5.5) in the two-year period centred on maternal death. This study demonstrated that HIV impacts on infants through vertical transmission but also through higher child deaths associated with maternal death.

Given that in several countries in Southern Africa large numbers of the population are faced with hunger, food insecurity and malnutrition, HIV further exacerbates the situation. In reviewing trends in child nutritional status in Lesotho, Malawi, Mozambique, Swaziland, Zambia and Zimbawe from 2001, it was found that areas of higher HIV/AIDS prevalence showed more deterioration in child nutrition, particularly due to the drought that was ongoing in these areas at this time. In addition it was found that the most vulnerable households in

these countries were in more modern areas nearer towns and resources needed to be directed to them.[152] Whether this finding would hold true in the South African context is not known.

A study was undertaken in Uganda to assess the extent to which HIV infection predisposes children with malnutrition to recurrent bacterial infections.[153] In following 134 severely malnourished children, 22.4% had bacteraemia, mainly those less than 24 months of age. The study did not find a significant difference in mean weight, height and MUAC among the children with bacteraemia and those without. They also found that bacteraemia was a significant prognostic indicator of death in children with severe malnutrition; however, there was no association between bacteraemia and HIV in their cohort.

A review of available data on child mortality in Africa according to the HIV status of the mothers and the children was undertaken.[145] The analysis of this data indicated that the MTCT rate varied from 15% to 45%, of which 15 to 20% is from breastfeeding. Based on child mortality estimates for community-based cohorts, children of HIV-infected mothers have higher mortality rates than children of uninfected mothers. This same data was expanded to estimate child mortality associated with reasons for non-breastfeeding and weaning. Child mortality rate for children never breastfed was 221.3 per 1000. The main reported reason for not breastfeeding cited by 63.9% of the mothers was preceding maternal-infant morbidity. They also found mortality to have been higher among children who were weaned because of preceding morbidity compared to those who were weaned for reasons other than health (19.2 per 1000 versus 9.3 per 1000) respectively. The authors extrapolated from their findings that mortality among those children who were voluntarily not breastfed or weaned could provide the best estimate of the potential risk if HIV-infected mothers decided not to breastfeed or to stop breastfeeding in order to prevent vertical transmission. Using their data they concluded that if infants born to HIV-

infected mothers are breastfed, they would expect 16% to become HIV infected and 0.9% to die (16.9%), resulting in a net HIV-free survival of 83.1%. However, if HIV-positive mothers voluntarily decided not to breastfeed the expected mortality would be 3.5% and the net HIV-free survival would be 96.3%. This would then imply a net positive benefit to HIV-free survival of 13.2% through self-selected avoidance of all breastfeeding.

The linkage between poor maternal health and HIV and child health outcomes has also been documented from urban medical centres in the USA. Data indicates that HIV-1-infected infants born to women with advanced HIV-1 disease were at increased risk for rapid disease progression.[13] Specifically, the researchers found that children born to mothers with CD4 cell counts above 100 000 copies/ml progressed more rapidly than children born to mothers with less advanced HIV disease, controlling for child antiretroviral therapy and year of birth.

According to the Ghent Group, 2001, whilst child mortality may be an outcome in PMTCT, in the conduct of any research in order to observe a "meaningful" difference in mortality a follow-up period of up to five years after birth is required. These authors suggest that an assessment of HIV-free survival may thus be an alternative to measuring HIV transmission risk only.[154]

### 2.3.4. Maternal caring capacity, psychosocial wellbeing and child growth

The caring capacity of HIV-infected mothers for their children may also be compromised by their own psychosocial state post-delivery. Others allude to growing interest in the scientific literature to establish whether depression and stress account for variability in HIV disease progression.[155] Further, it is mentioned that while there appears to be an association between depression,

stress and HIV disease progression, the actual biological mechanisms that precipitate this are not fully understood. More recent research acknowledges, however, that there is contradictory evidence on the association between depression and biomarkers of HIV disease progression, especially when the assessments are being carried out over a long period of time.[11] Other researchers[9] state that "the impact of depression on morbidity and mortality among women with human immunodeficiency virus (HIV) has not been examined despite the fact that women with HIV have substantially higher rates of depression than their male counterparts".

A longitudinal prospective study among HIV-infected women in the USA determined the association between depression and HIV-related mortality and disease progression (measured by changes in CD4 lymphocyte counts).[10] A standardised depression scale was applied in this research. It was found that women with depressive symptoms were twice as likely to die as women with limited depressive symptoms (Relative Risk [RR]: 2.0; 95% confidence interval [CI], 1.0-3.8). Amongst those women with CD4 cell counts <200cells/mm$^3$, HIV-related mortality was 54% if they were chronically depressed, for those with intermittent depression it was 48% and for those with limited or no depressive disorders it was 21%.

Overall it was found that the more depressed mothers displayed a greater decline in CD4 cell counts. Other authors have investigated the impact of depressive symptoms on more advanced HIV disease in women and found that those women who had chronic depressive symptoms were more than twice as likely to die compared to those with limited or no symptoms. AIDS-related mortality was highly likely amongst women who had low baseline CD4 counts, high viral loads and HIV-related symptoms at baseline.[12]

Data from Tanzania reported on depressive symptoms among HIV-infected women from pregnancy and followed them up for more than 12 months postpartum.[11] They found that during the follow-up period 57% of the women in the study had experienced some symptoms typical of depression. In addition, this study found an association between depression and HIV disease progression (HIV clinical stage 3/4 [HR = 1.61, 95% CI: 1.28 to 2.03] and mortality [HR = 2.65, 95% CI: 1.89 to 3.71].

### 2.3.5. Summary

This review assists in linking the maternal wellbeing, health and nutritional status to the mother's ability to care for her newborn child. HIV-infected women may, due to their disease state, display increased levels of depression and poor coping ability with their maternal role by virtue of their diagnosis. In addition, it is clear that there is an interaction between the psychosocial wellbeing of a mother, her HIV disease progression and also her caring capacity for her child.