RANDOMISED PLACEBO-CONTROLLED TRIAL TO EVALUATE THE EFFECT OF VITAMIN A ON MOTHER-TO-CHILD TRANSMISSION OF HIV-1 IN BLOEMFONTEIN

PERPETUAL CHIKOBVU

A thesis submitted in accordance with the requirements for the Doctor of Philosophy degree in the Faculty of Health Sciences, Department of Biostatistics at the University of the Free State.

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I declare that the thesis hereby submitted by me for the Doctor of Philosophy degree at the University of the Free State is my own independent work and has not previously been submitted by me at another University/Faculty. I furthermore cede copyright of the thesis in favour of the University of the Free State

PERPETUAL CHIKOBVU

SUMMARY

Mother-to-child (vertical) transmission is the primary means by which young children acquire human immunodeficiency virus type 1 (HIV-1) infection. Anti-retrovirals such as Zidovudine and nevirapine can reduce vertical transmission of HIV significantly, but this treatment is still largely unaffordable in Africa. Maternal vitamin A deficiency is suspected to enhance vertical transmission of HIV. Furthermore, vitamin A is known to act as a coenzyme to the immune process. Therefore, a double-blind randomized placebo controlled trial to assess the effect of vitamin A supplementation on vertical transmission of HIV was launched in Bloemfontein in 1997.

A total of 2949 pregnant women attending the antenatal clinics at Pelonomi and Universitas hospitals and the Mangaung University Community Partnership clinic were counselled for HIV testing, and 2543 were willing to be screened by HIV testing for possible inclusion in the trial. Of the women screened 595 (23.4%) were HIV positive, and 303 of these were willing to participate in the trial. 152 women were randomized to vitamin A treatment and 151 to placebo treatment. Patients were seen at 2 monthly intervals in the antenatal phase. Post-natally mother-infants pairs were seen when the infant was 1 month old, 3 months old, and thereafter, 3 monthly till 18 months old. A total of 191 patients (63% of all the study participants) missed one or more visits and had to be traced.

Of the 303 patients included in the study 158 had a conclusive infant HIV test result (patients in the Intention To Treat (ITT) analysis population) and 104 patients had a

conclusive infant HIV test result when the baby was 3 months old (patients in the Per Protocol (PP) analysis population). Of 158 patients, in the ITT population 73 were in the vitamin A group and 85 in the placebo group. Per treatment group the baseline characteristics of those in the ITT population and those who are not, did not differ significantly.

The HIV transmission rates were 19.2% and 21.2% for vitamin A and placebo groups respectively (ITT population). There is no statistically significant difference in the transmission rates between vitamin A and placebo groups (p=0.76). Overall, this study provides no evidence that vitamin A is effective in reducing vertical HIV-1 transmission rate.

There was no statistically significant difference in the percentages of HIV symptoms recorded at post delivery visit 1 through to the 18 months visit between the two treatment groups for either mothers or infants. A similar pattern was observed for the vital signs for the mothers. The full blood and T-cell counts were similar between the two treatment groups at all visits for both mothers and infants.

Only 4 patients reported adverse events; these were not related to the treatment. Twenty-six infants and one mother died during the study. The overall infant mortality rate was 85.8 per 1000 infant population. The infant death rates were approximately 11% in the placebo group and 6% in the vitamin A group (p=0.097). Thus, Vitamin A was associated

with a reduction in infant mortality, although not statistically significant. This association may be worth further investigation as there is potential for a substantial impact.

OPSOMMING

Moeder-na-kind (vertikale) oordrag is die algemeenste manier waarop jong kinders menslike immuniteitsgebrek virus tipe 1 (MIV-1) opdoen. Antiretrovirale middels soos Zidovudine en nevirapine kan die vertikale oordrag van MIV betekenisvol verlaag, maar hierdie behandeling is steeds meestal nie bekostigbaar in Afrika nie. Daar word vermoed dat moederlike vitamine A gebrek die vertikale oordrag van MIV bevorder. Verder is dit bekend dat vitamine A 'n ko-ensiem is tot die immuunproses. Daarom is 'n gerandomiseerde dubbelblinde plasebo gekontrolleerde proef om die effek van vitamine A supplementasie op die vertikale oordrag van HIV te bepaal in 1997 in Bloemfontein van stapel gestuur.

'n Totaal van 2949 swanger vroue wat die voorgeboorteklinieke by die Universitas en Pelonomi Hospitale en die Mangaung University Community Partnership Project kliniek bygewoon het, het berading vir MIV-toetsing ontvang, en 2543 was bereid om deur MIV-toetsing gesif te word vir moontlike insluiting in die proef. Van die vroue wat gesif is, was 595 (23.4%) MIV-positief, en 303 van hulle het ingewillig om aan die studie deel te neem. 152 MIV positiewe vroue is gerandomiseer om vitamine A behandeling te ontvang en 151 plasebo behandeling. Pasiënte is tydens die voorgeboorte fase 2 maandeliks gesien. In die nageboorte fase is moeder-baba pare gesien toe die baba 1 maand oud was, 3 maande oud en daarna 3 maandeliks tot 18 maande oud. 'n Totaal van 191 pasiënte (63% van al die studiedeelnemers) het een of meer besoek gemis en moes opgespoor word.

Van die 303 vroue wat ingesluit is in die studie, het 158 'n afdoende baba-MIV toetsuitslag gehad (pasiënte in die Beplan om te Behandel (BB) ontledingspopulasie) en 104 pasiënte het 'n afdoende baba MIV toetsuitslag gehad toe die baba 3 maade oud was (pasiënte in die Per Protokol (PP) ontledingspopulasie). Van die 158 pasiënte in die BB populasie was 73 in die vitamine A groep en 85 in die plasebo groep. Per behandelingsgroep was daar geen betekenisvolle verskille ten opsigte van die basislyngegewens tussen die vroue in die BB populasie en diegene nie in die BB nie.

Die MIV oordragskoerse was 19.2% en 21.2% vir die vitamine A en plasebo groepe onderskeidelik (BB populasie). Daar was geen statisties betekenisvolle verskil in die oordragskoers tussen vitamine A en plasebo nie (p=0.76). Hierdie studie lewer geen bewys dat vitamine A effektief is in die verlaging van die vertikale oordragskoers nie.

Daar was geen statisties betekenisvolle verskille tussen die twee groepe ten opsigte van die persentasies MIV simptome vir moeders of babas by die eerste nageboorte besoek tot by die 18 maande besoek nie. 'n Soortgelyke patroon is waargeneem vir die vitale tekens van die moeders. Die volbloed en T-sel tellings was soortgelyk tussen die behandelings vir alle besoeke vir moeders sowel as babas.

Slegs 4 pasiënte het newe-effekte gerapporteer, en dit het nie verband gehou met die behandeling nie. Ses-en-twintig babas en een moeder het gedurende die studie gesterf. Die algehele babasterftekoers was 85.5 per 100 babas. Die babasterftekoers was ongeveer 11% in die plasebogroep en 6% in die vitamine A groep (p=0.097). Vitamine A is dus

geassosieer met 'n verlaging in babasterftes, alhoewel nie statisties betekenisvol nie. Dit verdien verdere ondersoek aangesien die moontlikheid vir 'n groot impak bestaan.

Key terms:

HIV

HIV positive pregnant women

Vertical (mother-to-child) transmission

Randomised-controlled trial

Vitamin A supplementation

Vitamin A efficacy

HIV Transmission rates

Public health

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Chapter 1: INTRODUCTION

No region of the world has escaped the human immunodeficiency virus (HIV) epidemic but its worst effects have been felt in developing countries, particularly in Sub-Saharan Africa. The HIV pandemic has a profound impact on the health and survival of children in these regions. Almost all HIV infections among children are due to vertical (mother-to -child) transmission.[1] The majority of HIV infected children are born in the developing world,[1,2] and a crucial challenge is to identify safe, affordable, feasible and effective interventions aimed at reducing vertical HIV transmission in these countries.

1.1 The global and Sub-Saharan Africa HIV/AIDS epidemic

The rapid spread of HIV is claiming thousands of lives each year world-wide. Since the epidemic began, more than 60 million people have been infected with the virus.[2] The global number of people living with HIV has been estimated to be 40 million at the end of 2001. Of these, 28.1 million are living in Africa, 7.1 million in Asia and 1.4 million in Latin America (Figure 1.1).[2] Since the epidemic started, approximately 22.3 million AIDS deaths have occurred globally.[2] The lack of balance between the number of new infections and the number of deaths shows that the HIV positive population is still expanding, and approximately 5 million new infections occurred world-wide compared to 3 million estimated AIDS deaths, in 2001 alone.[2] Although Sub-Saharan Africa continues to be the worst affected region with 70% of the global total of infected people, it is home to just 10% of the global population.[1,2]

Sub-Saharan Africa is the only region where more women than men are infected.[1] Since the epidemic began, 83% of all AIDS deaths have occurred in this region and this number is expected to continue increasing for some years to come. In 2001 alone the region experienced 3.4 million new infections and about 2.3 million AIDS deaths.[2] The proportion of people with AIDS is thus increasing in this region where poverty, poor health systems, limited resources for prevention and care, contribute to the spread of the virus.

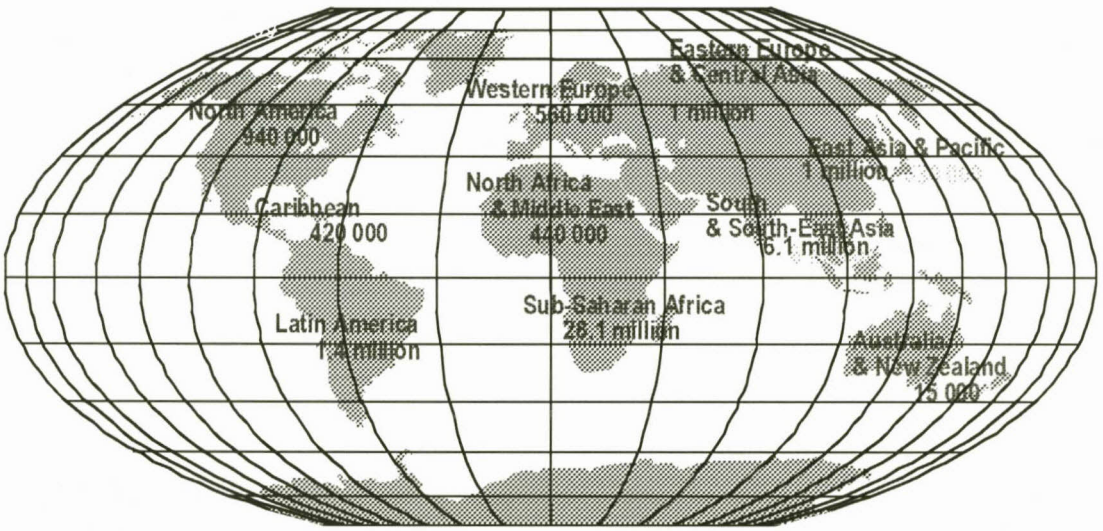

Figure 1.1 Estimated number of HIV-infected people globally, and geographical distribution of cases, at the end of 2001.[2]

The estimates of the effects of the HIV/AIDS epidemic globally and in Sub-Saharan Africa are shown in Table 1.1. At the end of 2001, UNAIDS/WHO estimated that about 17.6 million women were living with HIV/AIDS globally[2] and 95% were of child-bearing age. At the end of 1999, approximately 80% (12.2 million) of 14.8 million infected

women were from Sub-Saharan Africa.[3] At the end of 2001, an estimate of about 2.7 million children (< 15 years) were infected with the virus and approximately 89% of these were living in Sub-Saharan Africa.[2] Thus the prevalence of HIV infection among children is increasing in a manner that closely follows the spread of the disease among women. This increase is mainly because preventive anti-retroviral therapies are not available to pregnant women in the region.

Furthermore, UNAIDS estimated that HIV/AIDS killed at least 6.2 million women world-wide by the end of 1999[3], while approximately 1.1 million died from AIDS in 2001 alone. An estimate of 4.88 million children died from AIDS world-wide since the beginning of the epidemic and about 0.58 million died in 2001 alone (Table 1.1).[2] Clearly the major challenge in Sub-Saharan Africa is to get the balance between prevention and care right. This balance is almost impossible at this stage due to the collapse of the economies of many of the countries in the region.

Table 1.1
UNAIDS estimates of HIV /AIDS epidemic

	People living With HIV/AIDS	New infections In 2001 alone	Cumulative deaths since epidemic began	Deaths in 2001 alone
Global	40.000	5.000	22.300	3.000
Africa	28.540	3.480	18.524	2.330
Sub-Saharan Africa	28.100	3.400	18.400	2.300
Adults	37.200	4.300	17.420	2.400
Women	17.600	1.800	6.200*	1.100
Children	2.700	0.800	4.880	0.580

*Figures compiled from UNAIDS estimates[2] and are in millions. * An estimate for up to end of 1999*

AIDS is the leading cause of death in Africa compared to other diseases, for example, tuberculosis and lung cancer. It was responsible for 19% of deaths in Africa and 4.2% globally in1999 (Figure 1.2).[3] Therefore prevention measures must focus on AIDS.[3] In this medically resource-constrained region, an important challenge is the prevention of new infections through behavioural modification strategies, since inadequate medical infrastructure and costs indicate that the health care capacity will continue to lag behind. However, prevention may be hampered by the complexities in African societies where people still do not want to talk about this deadly disease which has caused immense suffering within the communities.

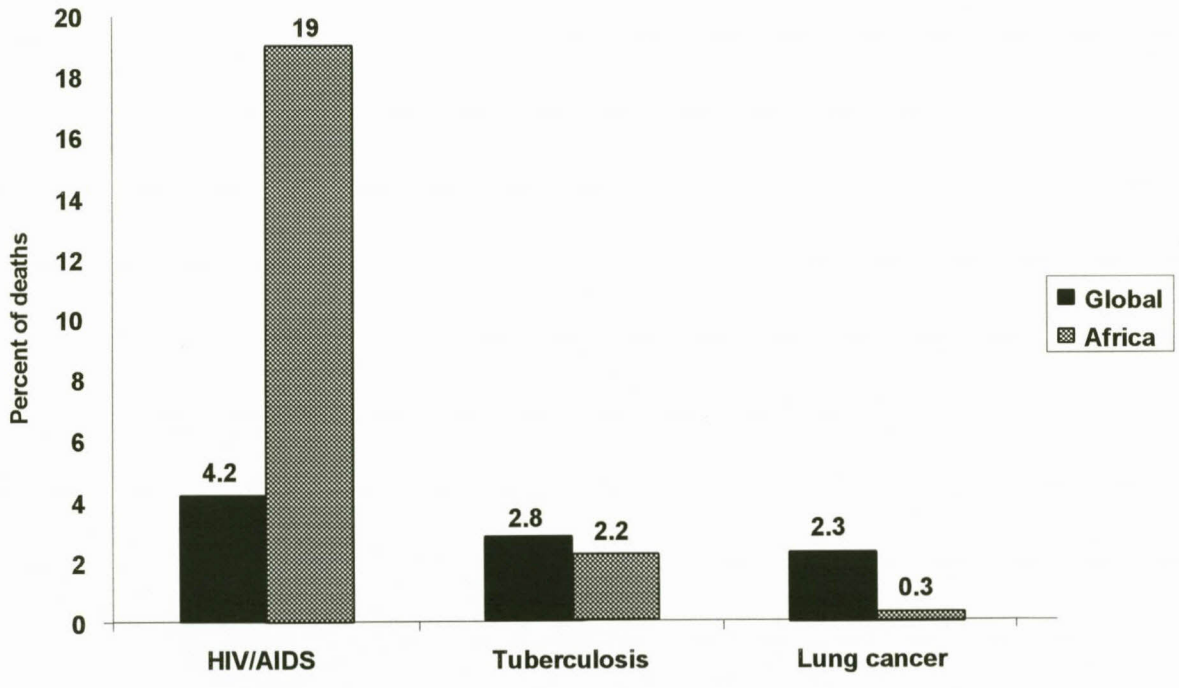

Figure 1.2. Causes of deaths globally and in Africa[3]

1.2 The epidemic in South Africa

South Africa, which trailed behind some of its neighbours in HIV infection levels at the start of the 1990s,[3] has moved rapidly from a hidden epidemic to a very visible HIV epidemic. South Africa is now the country with the highest number of people with HIV/AIDS in the world.[1] At the end of 2001 it was estimated that 4.74 million people were infected with HIV in this country alone; approximately 55.9% of the 4.74 million are women of child-bearing age.[4] It is estimated that in 2000 one in nine South Africans were HIV positive.[2,4] The bulk of new infections on the continent continue to be concentrated in Southern Africa. It was believed that one in seven new infections on the continent in 1998 were in South Africa.[3]

HIV/AIDS is, therefore, one of the most severe health problems facing South African women. The National HIV Surveys in South Africa demonstrated that among women presenting for antenatal care in public health facilities, the prevalence of HIV infection has tremendously increased from <1% (1990) to 22.8% (1998) and 24.8% (2001).[4] Figure1.3 shows that the national prevalence rate increase has stabilized somewhat since 1998. The greatest increase, however, was experienced between 1997 and 1998 (Figure1.3).[4] The large increase in the epidemic among pregnant women (Figure 1.3)[4] may eventually result in South Africa having the highest HIV prevalence rate in the continent. The epidemic is clearly awesome in magnitude and its impact on the country at the beginning of the 21st century.

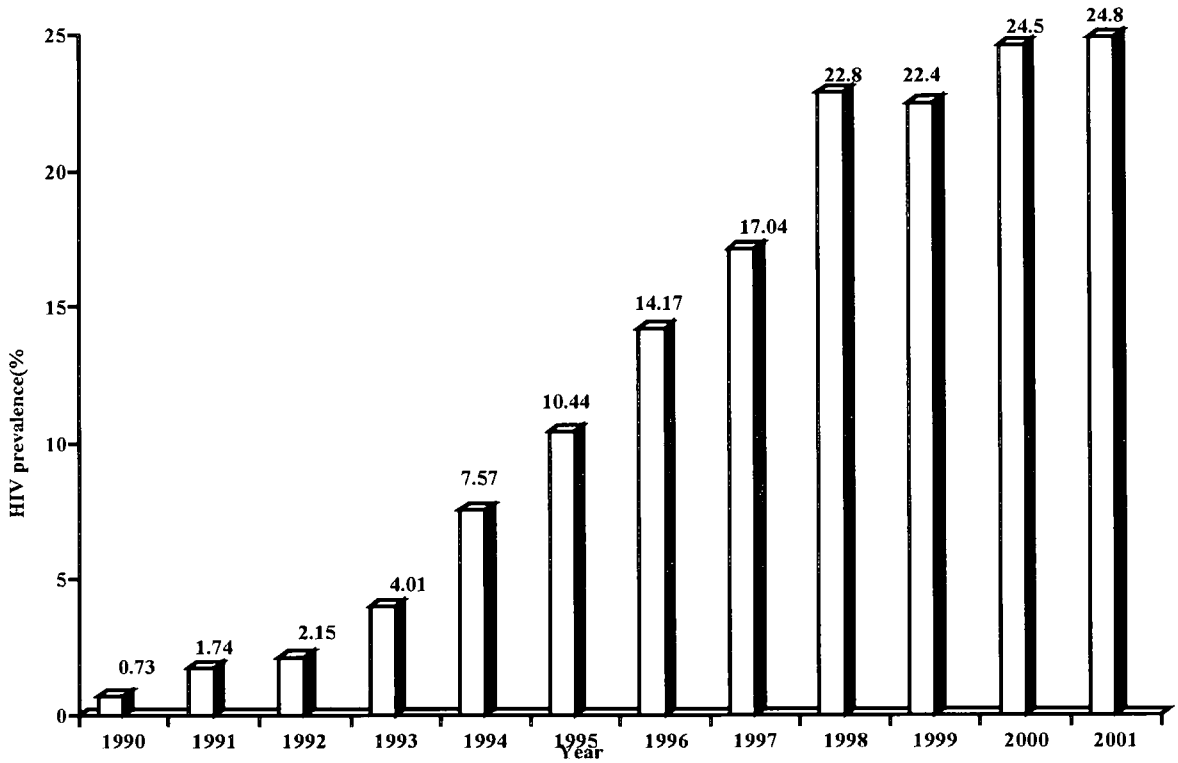

Figure 1.3. The increase in HIV seroprevalence from 1990 to 2001 in women attending antenatal clinics in South Africa[4]

The details of geographical and age distribution of HIV prevalence in antenatal women are given in Tables 1.2 and 1.3, respectively. It is clear that the epidemic has affected all nine South African provinces. The highest sero-prevalence in 2001 was in Kwazulu Natal (33.5%) followed by the Free State (30.1%), Gauteng (29.8%) and Mpumalanga (29.2%).[4] All the provinces have experienced a marginal increase between 2000 and 2001 except Mpumalanga and Western Cape where there was less than 1% decrease from 2000 as well as Kwazulu Natal with approximately 3% decrease. Of the nine provinces six have already reached a seroprevalence of more than 20% among antenatal women (Table

1.2). In the Free State, the prevalence of HIV infection among antenatal clinic attendees was 9.2% (1994), 22.8% (1998) and 30.1% (2001) which shows a dramatic rise from the 0.6% reported in 1990.[4]

Table 1.2. HIV seroprevalence in antenatal clinic attendees by province in 2000 and 2001[4]

	HIV prevalence (%) and 95% confidence interval	
	2000	**2001**
KwaZulu/Natal	36.2 (33.4-39.0)	33.5 (30.6-36.4)
Mpumalanga	29.7 (25.9-33.6)	29.2 (25.6-32.8)
Gauteng	29.4 (27.9-31.5)	29.8 (27.5-32.1)
Free State	27.9 (24.6-31.3)	30.1 (26.5-33.7)
North West	22.9 (20.1-25.7)	25.2 (21.9-28.6)
Eastern Cape	20.2 (17.2-23.1)	21.7 (19.0-24.4)
Limpopo	13.2 (11.7-14.8)	14.5 (12.2-16.9)
Northern Cape	11.2 (8.5-13.8)	15.9 (10.1-21.6)
Western Cape	8.7 (6.0-11.4)	8.6 (5.8-11.5)
National	24.5 (23.4-25.6)	24.8 (23.6-26.1)

Despite public awareness campaigns, there still was an increase in seroprevalence in young women aged 25-39 (Table 1.3). This peak indicates that the campaigns are not having an impact on mothers in this age group. Therefore alternative strategies aimed at women in their mid twenties to late thirties must be investigated.

Table 1.3. HIV seroprevalence in antenatal clinic attendees by age group in 2000 and 2001[4]

	HIV prevalence (%) and 95% confidence interval	
	2000	**2001**
<20	16.1 (14.5-17.7)	15.4 (13.8-16.9)
20 – 24	29.1 (27.4-30.8)	28.4 (26.5-30.2)
25 – 29	30.6 (28.8-32.4)	31.4 (29.5-33.3)
30 – 34	23.3 (21.5-25.1)	25.6 (23.5-27.7)
35 – 39	15.8 (13.9-17.7)	19.3 (17.0-21.5)
40 – 44*	10.2 (6.9-13.3)	9.1 (6.2-11.9)
45 – 49*	13.1 (2.09-24.0)	17.8 (4.3-31.4)

** The wide confidence intervals are a reflection on the small number of samples from older women included in the survey.*[4]

The sharp increase in HIV prevalence in antenatal clinics in selected provinces in South Africa is clearly shown in Figure 1.4.[4] HIV prevalence slightly decreased in Kwazulu-Natal between 2000 and 2001 although it is still the highest of all provinces. The prevalence for the Free State has continually increased from 1997 to 2001. In Mpumalanga the prevalence decreased between 1998 and 1999 and increased thereafter. The epidemic is thus still growing, especially among women and children. This epidemic will therefore continue to impact on the heavily burdened South African health system for some years to come unless preventive measures are put in place and take effect.

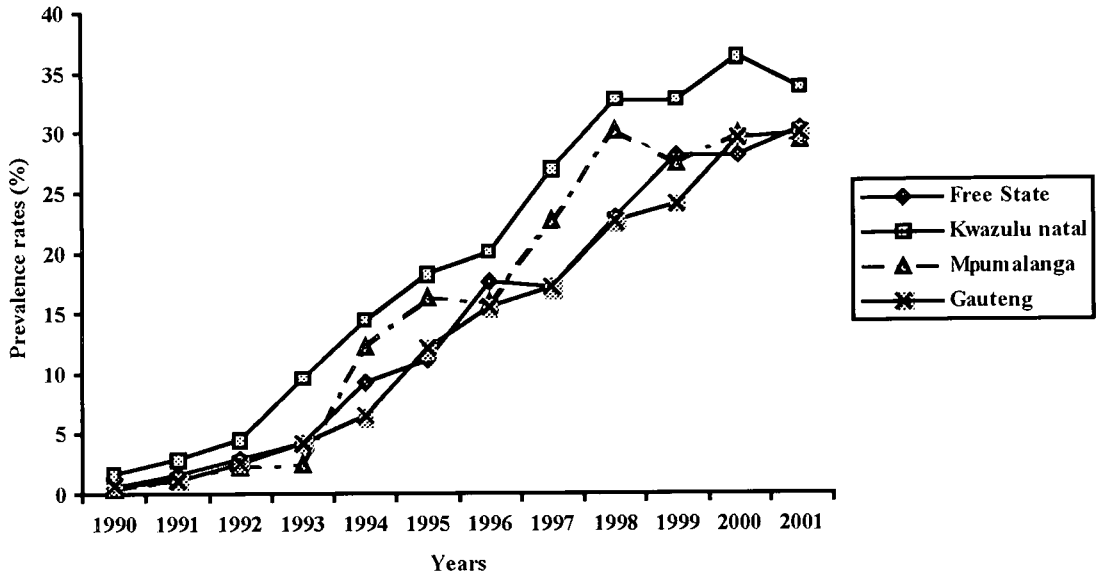

Figure 1.4. HIV prevalence among antenatal clinic attendees for leading provinces 1990 to 2001

Groeneveld and Padayachee estimated that by the year 2000 about 27% of the total adult black population in South Africa would be HIV positive.[5] The 1998 estimate was more than 7.5% of the total population.[6] One study indicated that about 69% of HIV infected individuals come from the urban black community whereas about 20% come from the rural black community.[7] Altogether, these figures demonstrate that HIV/AIDS poses a major threat to all South Africans, and especially to the black community. It was reported that more than half of all adults admitted to acute medical services in public hospitals in KwaZulu-Natal in 1998 were HIV positive.[6] Provincial health systems can no longer ignore the increasing burden of the disease and the impact it is having on staff, expenditure and ability to provide a service.

In 1992 paediatric AIDS accounted for 14% of AIDS cases in South Africa.[8] The high rates of infection, together with high rates of pregnancy among women have resulted in a

rapid increase in HIV positive children. In 1998, it was reported that 25% of all children admitted to the paediatric medical services in KwaZulu-Natal were HIV positive.[6] The spread of the disease among children closely follows the spread of the disease among women. UNAIDS estimated that by the year 2010 South Africa will be home to more than 2 million AIDS orphans (Figure 1.5).[3] Although prevention of new infections remains an important challenge, it is crucial to find a balance between prevention and care strategies. One way of achieving this balance is through finding affordable strategies aimed at reducing vertical HIV transmission. Reducing the number of infected children will reduce the care burden in future.

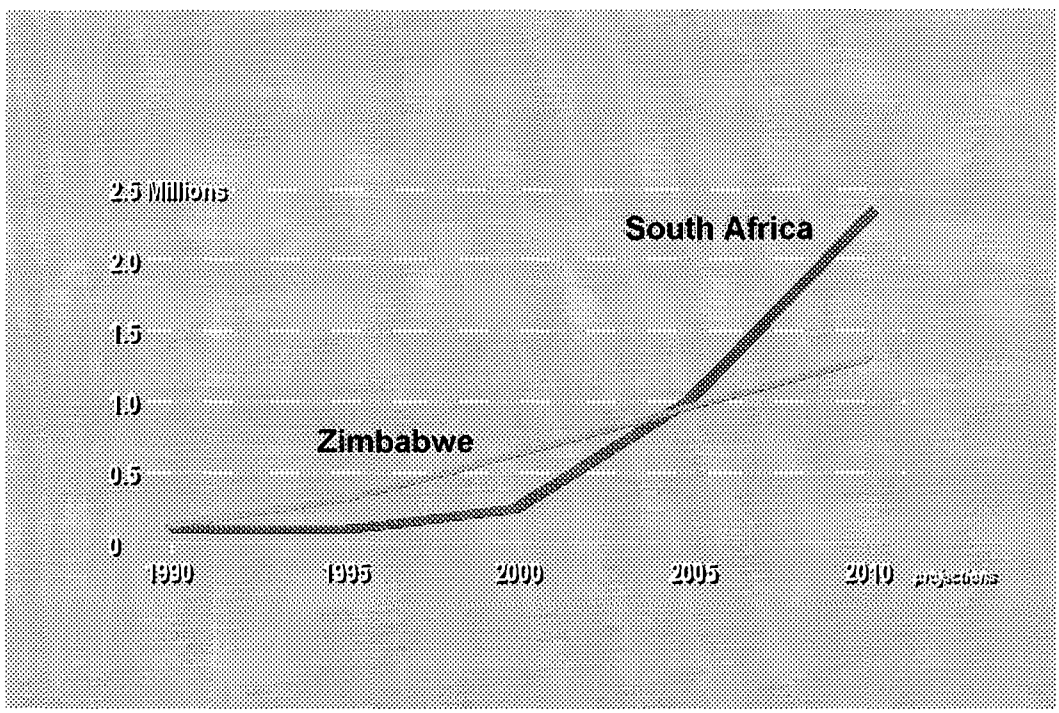

Figure1.5. Orphans due to AIDS, 1990-2010[3]

1.3 Vertical transmission rates of HIV-1

Reported rates of vertical HIV transmission differ significantly between developed and developing countries.[9] In developing countries, a child born to an HIV-infected mother has a 1-in-3 chance of being born infected [10], and nearly 80% of those infected will die before 5 years of age due to HIV-aggravated malnutrition, diarrhoea and respiratory infections. The overall vertical transmission rates of HIV have been reported at 20-42% in Africa, in contrast to 10-25% in the USA and Europe.[11,12,13,14,15,16,17,18,19,20,21] A systematic review of epidemiological studies on transmission via breast milk by Dunn *et al* showed an average transmission rate estimate of 29% (95% CI 16-42%)[22] for mothers who acquire HIV after delivery. In a breast-feeding population, the additional risk of HIV transmission through breast-feeding, over and above infection prior to or during birth is approximately 14% (95% CI 7-21%)[11,21,22,23] for mothers who were infected prenatally. Coutsoudis *et al* found that in infants who were exclusively breast fed for 3 months, the estimated proportion of HIV-1 infection was lower (14.6%) than that of infants who received mixed feeding (24.1%) for the same period.[24] Overall, the transmission rates in untreated non breast-feeding populations have ranged from 14% to 32% in industrialized countries versus 25% to 48% among breast-feeding population in resource poorer settings.[20]

1.4 Vertical transmission routes

Vertical transmission is the primary means by which young children become infected with human immunodeficiency virus type 1 (HIV-1).[16,17, 19, 25,26,27,28] Transmission can take place either in utero, during labour and delivery, or post-natally through breast

feeding.[13,15,17,22,29,30,31,32,33,34,35] However, the relative contribution of each of these routes remains poorly quantified. The exact time of transmission during pregnancy, delivery or lactation has been difficult to determine precisely.[27,31] HIV has been isolated from placental cells, foetal cord blood, neonatal blood specimens and amniotic fluid[31,36,37,38] but the pathway by which the virus enters the amniotic fluid is unknown.[31] Maury *et al* detected HIV in foetal-derived placental tissues as early as 9-11 weeks of gestation.[38] Transmission may thus already occur during the early stages of pregnancy.

Some studies suggested that most (50% to 80%) vertical transmission of HIV takes place around the time of birth.[21,26,39] Simonon *et al* found that 30.5% of 47 HIV infected children in Kigali (Rwanda) had an HIV positive PCR on cord blood.[36] This finding suggests that a substantial number or perhaps even the majority of transmissions occurred during pregnancy, although it is still not clear at what stage of pregnancy the foetus is most vulnerable to HIV transmission and infection.[17,37] They also found that some children with negative PCR on cord blood had a positive PCR on the blood samples collected at 3 months of age,[36] which also suggests the possibility of transmission occurring during breast feeding. Maternal plasma HIV viral load appears to be the best predictor of vertical HIV transmission.[21] In the absence of anti-retroviral therapies, studies have reported perinatal HIV transmission in 21% and 63% of mothers with mean viral load during pregnancy of < 100 000 and >100 000 copies/ml respectively.[21] Although maternal viral load is very useful for determining the risk of transmission, there is no level above which transmission always occurs nor level below which transmission is never seen.[21]

HIV transmission through breast-feeding has been documented in several studies.[13,15,17,24,26,27,29,30,35] The highest risk appears to be associated with women who acquire HIV after delivery when the consequently high viral load in the blood during primary infection will also cause a high viral load in the breast milk.[9,29,32] Datta *et al* found that prolonged breast-feeding was associated with an increased risk of infection in Nairobi.[16] HIV p-24 antigen has been detected in colostrum[29], which may indicate the presence of actively replicating viruses. In general, the risk of HIV transmission through breast-feeding is a great dilemma for many developing countries where 20% to 30% of lactating women are HIV positive,[13,16] and breast-feeding is the pillar of child survival associated with reduced morbidity and mortality from infectious diseases. Breast-feeding provides inexpensive infant nutrition particularly in Africa. Although unable to quantify very early transmission due to breast-feeding, Miotti *et al* reported cumulative transmission risk from breast-feeding in Malawi to be 3.5% at 6 months, 7% at 12 months, and 10.3% at 24 months.[35] In a clinical trial in Nairobi, Kenya, formula feeding by cup reduced postnatal transmission by 44% at the age of 2 years in the absence of anti-retroviral therapies,[23,40,41] and 75% of breast-milk transmission occurred during the first 6 months of life.[23,40]

1.5 Breast-feeding practices

In developed countries, where most people can afford to formula feed their infants, HIV infected women are discouraged from breast-feeding their infants.[10,29,30] However, in the developing world where the most common causes of death in infants are malnutrition and infectious diseases, the WHO has recommended that women breast-feed their infants

irrespective of the mother's HIV status.[10,30] In most developing countries, the discouragement of breast feeding is associated with significant increases in rates of diarrhoea with associated morbidity, and up to four fold increases in mortality[30,32,42], thus out-weighing even the 10-14% increased risk of HIV transmission. However, as it has become increasingly clear that the risk of transmission during breast-feeding may be substantial, many obstetricians in developing countries are weighing the potential benefits of breast feeding (which still outweigh the risk of HIV transmission) for individual women. Some women are counselled to breast feed their babies and some, i.e. those who can afford it, are advised to formula feed their babies. Complicating the issue even further is the fact that most African women do not know,[1] and do not want to know, their HIV status. One study has found that 50% of adult Tanzanian women know where they could be tested for HIV, yet only 6% have been tested.[1] In Zimbabwe, only 11% of adult women have been tested for the virus.[1] Therefore, breast-feeding policies must be made weighing the advantages and disadvantages for individual patients and the population as a whole.

1.6 Vitamin A deficiency

Vitamin A deficiency may lead to immunodeficiency disorders, which may cause pathological alterations in mucosal surfaces, changes in lymphocyte subpopulations and alterations of T and B-cell function.[42] Vitamin A and its metabolites are immune enhancers as they are micronutrients essential for immunity, cellular differentiation, maintenance of epithelial surface growth, reproduction and vision.[42,43,44,45] These general observations demonstrate the central role of vitamin A in immunity and resistance to

infection. Vitamin A deficiency may be a cofactor for the initiation and progression of HIV infection,[42,46] and it is common during infection[42], even in developed countries.

1.7 The potential role of maternal vitamin A deficiency on mother-to-child HIV transmission

Vitamin A deficiency during pregnancy and lactation, as evidenced by night blindness, is being increasingly recognised as a prevalent problem in many developing regions.[45] Clinical studies in India reported that night blindness was frequently found during the third trimester of pregnancy[45], and the prevalence of night blindness in the Jumula population group was 52%.[45] Some studies have demonstrated that vitamin A deficiency among HIV positive women is associated with a higher viral load in breast milk.[47,48] One study found that there was no increase in viral load after vitamin A treatment in the vitamin A group but they found a significant increase in viral load in the placebo group.[49]

Two studies have shown that vitamin A deficiency is common in HIV-infected pregnant women in developing countries.[45,43] Semba *et al* found that maternal vitamin A deficiency in Malawi was associated with vertical transmission of HIV.[46] Some studies in South Africa have shown that HIV/AIDS patients in the Free State province are malnourished and have low intake of several micronutrients including vitamin A.[50,51] Thus supplementation of vitamin A to HIV positive women in this population may improve their vitamin A status and subsequently their immune status. Vitamin A supplementation is cheap and simple to administer, and may reduce the severity of infectious disease episodes and perhaps prolong life.

Decreased serum retinol concentration (<1.05 μmol/l), a sensitive and responsive indicator of maternal vitamin A deficiency (biological functions are compromised below this level)[46], is substantially more common in developing countries compared to developed countries.[46] Women may be at greater risk of vitamin A deficiency during pregnancy or the year following pregnancy.[45,46] Among Malawian HIV positive mothers, Semba *et al* found that as maternal serum retinol concentrations fell (< 1.05 μmol/l)[46], the rate of infection in their infants increased from 7% in women with the highest vitamin A concentrations to 32% in those with the lowest.[46] This finding suggests that vitamin A status plays an important role in vertical transmission of HIV.

Vitamin A supplementation to women improves maternal vitamin A status and increases the vitamin A content of breast milk (for lactating mothers), thereby improving the vitamin A status of breast fed infants.[43,45] Several mechanisms may be at work as vitamin A is essential for immunoglobulin production, for natural killer cell activities, and for the production of several cytokines.[42] Vitamin A deficiency is associated with immunodeficiency disorder which results in alterations in immunity such as changes in lymphocyte subpopulations and altered T and B cell function as well as mucosal surfaces.[42] Vitamin A also enhances the immune system and has the potential to help antibody responses to T cell dependent antigens as well as to restore the integrity and function of the mucosal surfaces.[42] Therefore maternal vitamin A deficiency may result in a diminution in any of these processes leading to a decreased ability of the immune system to suppress the viral load. Maternal vitamin A supplementation may reverse these processes thereby minimising vertical HIV transmission.

1.8 The impact of vitamin A supplementation on immunity and infant mortality

Providing vitamin A to infants has also been suggested as supplementation may substantially reduce early infant mortality [48,52,53] as a result of improved immune function. Several clinical trials have demonstrated that vitamin A supplementation reduced severe morbidity and mortality from infectious diseases (e.g. gastrointestinal diseases) among children who come from areas in which vitamin A deficiency is endemic.[48,52,53,54] Vitamin A deficiency is however not endemic in South Africa. If a vitamin A deficient patient is identified in South Africa the physicians recommend vitamin A supplements (personal communication with local clinic staff at Pelonomi hospital). A study done in Indonesia found that supplementation of vitamin A to infants without HIV reduced child mortality by 34%.[42] In Durban, South Africa, intensive vitamin A supplementation of infants born to HIV infected women significantly reduced overall morbidity and mortality.[52] Among HIV infected children, vitamin A supplementation was associated with an estimated reduction of 49% for all diarrhoea, 56% for diarrhoea lasting 7 or more days and 77% for hospital admissions for diarrhoea.[52] However, vitamin A supplementation of babies born to HIV infected mother is not currently recommended as a program in South Africa. Infant vitamin A deficiency is treated like any other disease (personal communication with local clinic staff).

1.9 Vitamin A dosage

The International vitamin A Consultative Group set an upper limit of 10 000 IU/day for vitamin A consumption during pregnancy (for a period of 2 weeks[57]) to avoid

teratogenicity.[55,56,57] Several authorities have advised that pregnant women and women of child bearing age should not substantially exceed an intake of 8000 IU/day.[56] Obstetricians and Gynaecologists have recommended a maximum dose of 5 000 IU/day prior to and during pregnancy.[56] Supplementation of neonates with one dose 52 μmol (50 000IU) of vitamin A and young infants during immunisation with 26 μmol (25 000IU) has been recommended.[44] This dose was confirmed by a placebo-controlled trial among 2067 Indonesian neonates carried out to assess the safety and health impact of supplementation with 50 000IU oral dose of vitamin A on the first day of life.[44] The single dose of vitamin A administered on the first day of life was well tolerated. Acute side effects following this intervention were rare and mild. A randomised trial carried out in Durban administered a daily dose of vitamin A of 5 000 IU retinyl palmitate and 30mg β-carotene to pregnant women. Treatment commenced between 28 and 32 weeks gestation. Women in the vitamin A group received a dose of 200 000 IU retinyl palmitate at delivery.[58] No side effects were reported. In addition, this dose was associated with a reduction in the incidence of pre-term deliveries from 17.4% to 11.4%.[58]

Another study carried out in Durban gave 50 000IU to infants at the age of 1 and 3 months, 100 000IU at the age of 6 and 9 months and 200 000IU in conjunction with vitamin E as an antioxidant at the age of 12 and 15 months.[52] These doses reduced infant morbidity with an odds ratio (OR) of 0.69 (95% CI 0.48, 0.99). No side effects were reported. For lactating mothers, the WHO recommended a dose of 200 000IU.[57] However, one trial has reported no side effects when a dose of 300 000IU was given to

mothers in the post-partum period.[43] Pre-school children have been safely given 200 000IU every three to six months for many years.[44]

1.10 Study design

Our study was designed to determine the effect of oral vitamin A as opposed to placebo given to HIV positive pregnant women, subsequently lactating and non-lactating mothers and their infants on vertical transmission of HIV-1. This study was a double-blind, randomised, placebo controlled trial of 303 pregnant women who were randomly allocated to the treatment (vitamin A) or control (placebo) groups. Infants received active or control treatment depending on the randomised treatment of their mothers. The treatment ran through two Phases. Phase I was from randomisation (women between 12 to 26 weeks pregnancy) to delivery, and Phase II was from delivery up to when the infant was 18 months old, when children normally lose antibodies passively transferred from their mothers.[59] The placebo arm was included in this study because the standard clinical care in South Africa at the time of the study did not provide anti-retroviral drugs or vitamin A supplementation to HIV positive pregnant women or babies. De Cock, *et al* stated that researchers have an obligation to provide the best level of care that is practically attainable in the host country, not the level of care available in industrialized countries.[20] Furthermore, the efficacy of our intervention can best be judged when compared with no intervention at all (i.e. the standard care in South Africa at this stage). However, the mothers in the placebo group also received some benefits such as good clinical care by experienced physicians, any problems identified during follow-up were treated or referrals were made when necessary.

1.11 Rationale for the study

The results of the ACTG (AIDS Clinical Trials Group) 076 trial, released in early 1994, showed that Zidovudine (or AZT) administered to HIV infected pregnant women and their newborns reduced the transmission rate by about two-thirds.[28, 60,61] A study carried out in Thailand demonstrated that a short course of twice daily Zidovudine used from 36 weeks gestation until delivery reduced the risk of vertical transmission of HIV-1 by approximately one-half.[62] Similar studies performed in Africa observed 30% to 59% reduction of vertical transmission.[63,64,65] A study carried out in Uganda has shown that vertical HIV-1 transmission can be effectively decreased in breast fed African children with a short course maternal regimen of oral AZT or nevirapine.[66] Elective cesarean section was also found to reduce the transmission of HIV-1 from mother-to-child independently of the effects of treatment with Zidovudine.[67,68] However, the implementation of these strategies in Africa is hampered by financial constraints.[69,70,71] Vertical transmission of HIV, therefore, remains a serious problem for many developing countries, particularly in Africa, where antenatal HIV sero-prevalence ranges between 5% and 40%[41] and the majority of HIV positive mothers can not afford AZT or nevirapine.[69,70,71] This study was done before the nevirapine HIVNET102 data[66] became available. In addition, concern for potential toxic effects[40,72,73] of anti-retrovirals has slowed the implementation of anti-retroviral prophylaxis programmes in South Africa.

Any affordable, safe and implementable intervention in the African setting regarding the transmission of HIV from mother-to-child should thus surely be thoroughly investigated. In addition with-holding breast feeding in Africa will result in a significant increase in

infant mortality, since many mothers do not have access to tap water, electricity and some simply cannot afford to artificially feed their infants.[23,74,75] Hence, an intervention which reduces in utero, during delivery or labour and during breast feeding transmission of HIV from mother-to-child, and which can be applied universally, is needed. Intervention strategies designed to decrease mother-to-child HIV transmission in developing countries must consider potential means of reducing viral exposure during pregnancy and through breast feeding.

Intervention strategies must also consider the complex socio-economic and societal roots of the HIV epidemic,[76] especially in African black communities. The perception is, that if a person is known to be HIV positive, there is suspicion of promiscuity, as well as the stigmatization and discrimination associated with the infection within the community. Therefore interventions directed to all pregnant or lactating women, irrespective of their HIV status, may be the most effective and most feasible to implement programmatically in Africa.

Studies have shown that vitamin A deficiency is quite prevalent in HIV positive patients.[46,50] Vitamin A is also known to act as a coenzyme to the immune process.[42] Should vitamin A supplementation be found to decrease transmission, it would be much more economical and feasible to implement in Africa until such times when AZT and other medication become more freely available.

Although studies have been carried out to investigate the effect of vitamin A on pregnancy outcome and early vertical transmission when supplementing HIV positive pregnant women,[58,77] no published studies have continually supplemented both mother and infant. Our study is unique by attempting to implement the intervention during pregnancy and lactation to both mother and infant till the infant is 18 months old. Pregnancy-linked supplementation is logistically relatively easy to sustain in sub-Saharan African countries where HIV infection rates are high among women of reproductive age. Pregnancy is the time when the majority of women, even in the poorest countries, come into contact with the formal or informal health care system.

The study also addresses the aspects of the natural course of HIV and is the first to determine the vertical HIV transmission rate in Bloemfontein. The proposed intervention may also reduce the risk of HIV transmission to infants born to HIV positive mothers who have escaped infection during pregnancy and delivery. The present study is also unique in that it was the first to address the potential effects of vitamin A supplementation on the immune system of pregnant women in the Free State, South Africa.

Appendix 1 contains the one published article and one article in press arising from the study.

1.12 Research question and Objectives

Research Question

Does vitamin A supplementation to HIV positive pregnant women, subsequently lactating and non-lactating mothers and their infants reduce mother-to-child HIV transmission?

Objectives

PRIMARY

- To determine if oral administration of vitamin A to HIV positive pregnant women, subsequently lactating and non-lactating mothers and their infants reduces the mother -to-child HIV transmission rate.

SECONDARY

- To determine if an oral administration of vitamin A to these infants reduces infant morbidity and mortality.
- To determine the effect of Vitamin A supplementation on immune function.
- To determine the overall vertical transmission rate in this population.

Chapter 2: METHODS

2.1 Overall study design and plan

This study was designed as a double-blind, randomised, placebo controlled trial in 400 HIV positive pregnant women who were randomly allocated to the treatment (vitamin A) or control (placebo) group. Infants received vitamin A or placebo depending on the randomised treatment of their mothers. Patients were seen at 2 month intervals during pregnancy, when the baby was one and three months old, and at 3 month intervals until the baby was 18 months old.

2.2 Discussion of study design, including the choice of control group

The primary objective of the clinical study was to determine the effect of oral vitamin A supplementation as compared to placebo on vertical transmission of HIV-1 when given to HIV positive pregnant women, subsequent lactating and non-lactating mothers and their infants. Treatment was administered in two Phases. Phase I lasted from randomisation (12 to 36 weeks of gestation) to delivery, and Phase II lasted from delivery up to when the infant was 18 months old, when children normally lose antibodies passively transferred from their mothers.

Placebo was chosen as the control treatment in this study because at the time of the design and clinical conduct of this study (1997 to 2000) the standard clinical care in South Africa did not provide anti-retroviral drugs or any other treatment that effectively reduces vertical HIV transmission to HIV positive pregnant women or babies.

Furthermore, the efficacy of our intervention could best be judged when compared with no intervention (i.e. the standard care in South Africa at that stage).

Major outcomes were the comparison of the mother-to-child HIV transmission rates and infant mortality between the two groups. The infants' HIV status was evaluated by PCR, p-24 antigen testing and ELISA at 18 months to confirm positivity, depending on availability of blood.

2.3 Study population and area

The study was conducted in the urban area of Bloemfontein, Free State province, South Africa. HIV positive pregnant women were recruited from patients attending the Universitas and Pelonomi hospital antenatal clinics and the Mangaung University Community Partnership Program (MUCPP) antenatal clinic. The first patient was enrolled on the 15th of September 1997 and the last patient was enrolled on the 8th of April 1999.

2.4 Sample size estimation

The sample size calculation was based on the following assumptions:

Type I error of 5% (two tailed)

Type II error of 20%

Among HIV positive women receiving placebo, the mother-to-child HIV transmission rate was expected to be about 31% (the average of the range 14% to 48% stated by De Cock *et al*)[20] at 18 months of age, of which about 10% would have occurred as a result of

breast-feeding or during the postpartum period. Among HIV positive women receiving treatment, the mother-to-child rate of HIV transmission was expected to be about 10% at 18 months, of which about 5% would have occurred as a result of breast feeding. We wanted to show that the transmission rate was decreased by at least 10% by vitamin A. Therefore the following hypothesis and alternative were to be tested:

H_0: $P1-P2=\delta$; H_A: $P1-P2 \neq \delta$

The required sample size per treatment was estimated using the following formula

$$N=\{\frac{P1\,(100-P1)+P2(100-P2)}{(P1-P2-\delta)^2}\}\times f(\alpha;\beta)$$ [78,79]

where P1 is the expected transmission rate in the placebo group i.e. P1=31%

P2 is the expected transmission rate in the treatment group i.e. P2=10%

δ=10%

$f(\alpha;\beta)$ is the square of the sum of the upper tail β point and the upper tail $\alpha/2$ point of the standard normal distribution. From the given Tables $f(\alpha;\beta)=7.85$ with $\alpha=0.05$ and $\beta=0.2$ [78,79] for a two tailed test.

$$\therefore N=\{\frac{(31x69)+(10x90)}{(31-10-10)^2}\}\times 7.85 = 197.2$$

In round figures this number means two independent samples (treatment and control) each of 200 patients.

The prevalence of HIV infection among pregnant women attending antenatal clinics in Bloemfontein was approximately 20% at the start of the trial; about 4000 deliveries were

to be performed per year (personal communication with Professor HS Cronje, Department of Obstetrics and Gyneacology). Therefore about 800 women attending antenatal clinics were expected to be HIV positive per year.

2.5 Screening for HIV antibodies

Routine screening for the presence of HIV antibodies has been done at the antenatal clinic of the Universitas hospital since 1996. At the other sites used in this study (Pelonomi Hospital and MUCPP clinic) no routine screening existed. To identify possible participants for the study, voluntary HIV screening of patients attending the Pelonomi and MUCPP antenatal clinics was started in September 1997 and continued until January 1999. The same study doctor screened patients during their first antenatal care visit at the two study sites where routine screening was not available.

At Universitas hospital the routine HIV screening included pre- and post-test counselling. At Pelonomi and MUCPP pre-and post-test counselling was initiated for this study as part of the voluntary patient screening. At MUCPP pre-test counselling was done in groups by a male nurse doing post-graduate studies at the University of the Free State, or by a male counsellor working at MUCPP up to March 1998. Thereafter the clinic registered nurses conducted the group pre-test and individual post-test counselling. At Pelonomi the clinic registered nurses were involved in the counselling from the beginning of the study.

During counselling the patients were informed that the HIV prevalence rate in pregnant women in the area was about 20%. Patient information forms regarding the conduct of

the study were available in English, Afrikaans and Sotho (see Appendix 2). Each patient was provided with a copy of this form in the language of her choice. The patients were asked to give written consent for HIV testing (see consent form in Appendix 3) and to come back for their HIV test results after one week. Initially, only the study doctor gave HIV test results to patients but many patients did not come to collect their results on the day when the doctor was available at the clinic. To make results more accessible to patients the clinic staff started giving the results to patients. HIV positive patients were asked to return to the clinic on the day when the study doctor was available, so that they could be recruited into the study if they wished.

Sera were tested for the presence of HIV-1 antibodies using two commercial enzyme linked immunosorbent assays (ELISAs), the Vironostika HIV-1 and -2 (Organon-Teknika, South Africa) and Behring Enzygnost HIV-1 and -2 PLUS (Behringwerke, Marburg, Germany) test kits. The tests were done in the Diagnostic laboratory of the Department of Virology at the University of the Free State.

2.5.1 Patient recruitment

Patients were recruited during working hours when they attended the second antenatal care visit (after the HIV test results were available). One doctor and the Ph.D. student recruited all the patients. Patients were recruited on Wednesdays at Universitas hospital, Thursdays at Pelonomi hospital and Fridays at MUCPP clinic.

During pre-test counselling patients were informed of the study and of the risk of giving birth to an HIV infected baby. The recruiting doctor or registered nurses at each of the

three clinics did individual post-test counselling. During post-test counselling patients were asked whether they were willing to participate in the study. Each patient was informed about the aim, type and method of the study, tests to be administered, risks and benefits of the study, and that she may withdraw from the study at any time for any reason after having informed the Ph.D. student of her intention to withdraw.

2.5.2 Inclusion Criteria

An HIV positive pregnant patient was included in the study if she:

- Was willing to participate in the study
- Was attending Pelonomi, Universitas, or MUCPP antenatal clinics
- Was able to return for regular follow-up visits (two and three monthly)
- Was between 20 and 36 weeks gestation at recruitment
- Was able to comprehend the statement of informed consent (see Appendix 4)
- Was willing to sign the statement of informed consent (see Appendix 4)

2.5.3 Exclusion Criteria

An HIV positive pregnant patient was excluded from participation in the study if she:

- Had participated in another study with an experimental drug within 8 weeks of commencement of the clinical phase of this study
- Was attending antenatal clinics other than those mentioned above
- Had evidence of a psychiatric disorder, antagonistic personality, poor motivation, emotional or intellectual problems likely to limit the validity of consent to participate in the study, or limit the ability to comply with protocol requirements

- Has a history of hypersensitivity to vitamin A or any related medications

These criteria were assessed verbally.

2.6 Treatments

2.6.1 Treatments administered

Before delivery (Phase I)

To avoid potential teratogenicity, Tablets of 5000 IU per day of vitamin A (or matching placebo) were taken by the pregnant women in this study.

After delivery (Phase II)

Infants received vitamin A in liquid form and were given the medication orally using a syringe. Vitamin A doses of 50 000 IU were administered to neonates at 1 and 3 months, and 100 000 IU was administered at 6 and 9 months of age. Two hundred thousand (200 000) IU in conjunction with 50 IU vitamin E as an antioxidant was administered at 12 and 15 months of age. Infants in the placebo arm received an equivalent volume of distilled water. Vitamin A for mothers was in tablet form. Mothers were given a dose of 300 000 IU of vitamin A (or matching placebo) at the one month post-delivery visit and 200 000 IU of vitamin A (or matching placebo) at each of the following visits.

The doses for the patients in each phase of the study were based on the relevant literature (see section 1.9).

2.6.2 Identity of the investigational products

Before delivery (Phase I)

Vitamin A Tablets taken by the pregnant women were manufactured for this study by Pharma Natura, Johannesburg. The Institute for Industrial Pharmacy of the University of Potchefstroom manufactured similar placebo Tablets.

After delivery (Phase II)

Vitamin A Arovit dragees (Roche) were given to mothers in the treatment group and vitamin A Arovit ampoules (Roche) and vitamin E (Vitaforce) to their infants. Placebo Tablets for the mothers were manufactured by the Institute for Industrial Pharmacy of the University of Potchefstroom. Placebo for infants was distilled water.

2.6.3 Randomisation

The 3 digit patient ID numbers (001- 400) were randomly assigned to placebo or vitamin A using a SAS program[80] and random number generator. Randomisation was balanced and done in blocks of 8 patients to ensure that allocation of treatment was approximately balanced throughout the study. This unique 3 digit ID number was written on a sticker affixed to the plastic bag containing the medication. One of the study supervisors packed the study medication (vitamin A or placebo) into plastic medication bags according to the randomisation list. The packets of tablets with consecutive numbers (001 to 303) were given to the recruiting doctor. The patients were assigned consecutive numbers as they were enrolled into the study starting from 001. Once assigned, this number was the patient's unique study ID number. Each patient received a packet containing randomised

study medication. The infants received the same treatment (either vitamin A or placebo) as their mothers.

2.6.4 Drug administration

Each patient received a packet containing 60 tablets corresponding to the code to which her ID number had been assigned during pregnancy. The patient was to take one tablet daily in phase I of the study. After delivery each patient (mother) was given tablets to chew in front of the doctor at each visit. The infants were given treatment according to the treatment of their mothers. Treatment and control for the infants was in liquid form.

2.6.5 Blinding

Vitamin A and placebo tablets were similar in appearance. The doctors who were seeing the patients received pre-packed packets of tablets marked with study identity number, which they gave to patients as they were enrolled in the study. The Ph.D. student under supervision administered the mother and infant's medication in phase II of the study in order to keep the examining doctor blinded.

2.6.6 Prior and concomitant therapy

Concomitant medications received by the patients were to be recorded in the Case Record Form (CRF) (see Appendix 5). The generic names, dose and duration of the therapy were to be recorded on the appropriate page of the CRF, except for combination products where the trade names were to be recorded. No patient was withdrawn from the study due to concomitant medication.

2.6.7 Treatment compliance

During phase I, the study doctor administered the first tablets (vitamin A or placebo) to patients at recruitment. The patients were given diaries (see Appendix 6) and were asked to mark the date and approximate times in the diary whenever they took the tablets. They were also asked to return unused tablets and the diaries at the next visit. During phase II, the Ph.D. student under supervision administered the study medication at every visit to mother-infant pairs.

2.7 Removal of patients from therapy

Patients who missed two or more consecutive visits during the post-natal phase were withdrawn from the study, as well as those patients who withdrew their consent for any reason.

2.8 Observations, measurements and instructions

2.8.1 Enrolment visit

For patients who fulfilled the entry criteria and were willing to participate, the following observations and measurements were obtained and noted in a Case Record Form (see Appendix 5): a record of vital signs, medical history including obstetrical and gynaecological history, findings from a physical examination (for signs of HIV-1 related diseases), intended period of stay in Bloemfontein after delivery, demographic details (i.e. residential address, next of kin address, race and home language), maternal age, weight, height, and duration of gestation. Venipunture blood specimens were obtained for

determination of T-cell subsets and RPR status. Thirty milliliters of blood was obtained from the patients into blood tubes and transported to the laboratory.

Serum, plasma and peripheral blood mononuclear cells from each patient were stored at -70^0C in the laboratory.

After enrolment, the patients swallowed the first tablet (vitamin A or placebo) in the presence of the recruiting doctor who wrote down the study ID number from the medication bag in the appropriate place on the Case Record Form (see Appendix 5). Then the doctor handed the rest of the tablets to the patient. Receipt of the tablets by the patient was documented. The unique study number was recorded on all data collection forms and specimens to facilitate linkage of the data.

The patient was given a diary (see Appendix 6) identified by her study number. She was asked to mark the dates when she took the tablet, and to return the tablet packages and diary at her next visit. Both the doctor and the Ph.D. student, in case of a need for a home visit, recorded the patient's address. In addition to her usual antenatal visits, the patient was requested to report to the participating clinic in two months' time. She was given an appointment card (see Appendix 7) listing the date, day, time and the contact telephone numbers for the doctor and the Ph.D. student. The patient was asked to return to the clinic if she developed acute illness between visiting times. Patients who required in-patient therapy were admitted to the hospital.

2.8.2 Subsequent visits before delivery

The same doctor who recruited the patients saw them at 2 month intervals during pregnancy. At those visits the following information was recorded: visiting dates of the patients, record of vital signs, medical history and physical examination results, concomitant treatment, any adverse events encountered and other notes as appropriate for all participating patients at each visit during pregnancy. The patient received another packet of 30 or 60 pre-packaged tablets if those she received at the previous visit were finished. The next visit date and time were given to the patient. If delivery was anticipated within the next 2 months she was given an appointment for a post-natal visit.

2.8.3 Post delivery visits

The mother was asked to return to the participating clinic when the baby was one month old. These clinics were different from the antenatal clinics where patients were seen during pregnancy, but were also located at Pelonomi and Universitas hospitals. The patient was given an appointment card (see Appendix 7) and a transfer letter (see Appendix 8) at her last visit during pregnancy. Mother-infant pairs were seen on Mondays at Pelonomi hospital and on Wednesdays at Universitas hospital. MUCPP patients went to either Pelonomi or Universitas hospitals for the post-natal visits. At the post-natal follow-up clinics mothers were seen by any one of the four study doctors (the main study physician who also did the recruitment, two virologists and one physician hired for the purpose of the study) who was available that day.

At Universitas hospital a blood sample was taken from the baby by the pediatric registrar who was on duty that day, whereas at Pelonomi hospital infants were seen and blood sampling performed by the same pediatrician throughout.

The following information was obtained from the mother and the infant: physical examination results, medical history, adverse events, date and mode of delivery and weight. In addition, data on gender, length and head circumference of the infant, infant illness requiring medical care since birth, frequency of breast-feeding and use of complementary food were obtained when the baby was one month old. These variables were also obtained from mother-infant pairs during 3 monthly visits until the baby was 18 months old. Although it was planned to obtain milk samples, this plan was later abandoned as most mothers were not breast feeding.

Blood samples from both mother and infant were obtained and tested for HIV (infants) when the baby was 3, 6, 12, and 18 months old. Blood samples were originally planned to be taken when the baby was one month old, but this plan was subsequently changed due to a shortage of skilled manpower. The Ph.D. student under supervision administered the study medicine to both mother and infant at each post-delivery visit keeping the examining doctor blinded. Concomitant medications or treatment were documented. The patient was given money for transport and an appointment card (see Appendix 7) for the next visit with date and time. She was told to return to the clinic if she or the infant developed acute illness between visiting times. Mothers and children requiring in-patient

management due to other illnesses were admitted to the Pelonomi or Universitas hospitals.

Infant HIV tests

Serum or plasma was separated from infants' blood taken at 3, 6, 12 and 18 months and was stored at -70 °C at the Virology laboratory of the University of the Free State. HIV p-24 antigen was tested for on all available 3, 6, and 12 month samples of infants using Innotest® HIV Antigen mAB (INNOGENETICS) (an enzyme immunoassay (EIA) for the detection of p-24 core antigens of the human immunodeficiency virus type 1, group O and type 2 in human serum, plasma or cell culture (quantification was not done). All available 18 month infant samples were tested for antigen and antibodies to HIV in a parallel ELISA (see infant HIV results in Appendix 9) using Vironostika® HIV Uni-Form II Ag/Ab (ORGANON TEKNIKA) and Enzygnost® HIV Integral (DADE BEHRING).

HIV nucleic acid detection was performed on all available 3 month infant venous blood samples at the combined diagnostic Virology laboratory of the University of Cape Town, Groote Schuur Hospital and South African Institute of Medical Research. The Nuclisens HIV-1 QT assay (Organon Teknika, Boxtel, Netherlands) was used. This assay utilises the nucleic acid sequence-based amplification (NASBA) principle to amplify viral RNA. The input volume of whole blood varied between 50-200ul, depending on the available sample. RNA isolation, amplification and electrochemiluminescence detection were performed according to the manufacturer's instructions. At the lowest input volumes of

50ul, the limit of detection of the assay is approximately 800 copies/ml. This assay can be utilised as a quantitative assay but for the purposes of this study, samples were considered simply "positive" (RNA detectable) or "negative" (RNA below the limit of detection).

2.8.4 Efficacy and safety variables measured

2.8.4.1 Safety

The safety of vitamin A was assessed by its effect on vital signs and full blood counts. Vital signs (systolic blood pressure, diastolic blood pressure, heart rate and heart sound) were measured for the mothers at all the visits. Complete blood counts, including total lymphocyte counts, were done on all patients at recruitment as well as at the 3, 6, 12, and 18 month visits using a Technicon H* 1cell counter in the Hematology Laboratory at the University of the Free State. The patients' T-cell subset numbers were determined using a counter flow cytometer (EPICS Profile II) and tri-colour labelled monoclonal antibodies; CD3 PY-5, T8 FITC and T4 RD1, according to the manufacturer's instructions. The absolute CD4 and CD8 T-cell count was calculated by multiplying the percentage determined on flow cytometry by total lymphocyte count. Helper/Suppressor ratio was obtained by dividing Helper CD4 percent count by Suppressors CD8 percent count.

High Blood Pressure (HBP) was defined as DBP>=90 mmHg and/or SBP>=140 mmHg and/or on current treatment for hypertension.

2.8.4.2 Efficacy

Primary Efficacy

The effect of vitamin A on reducing mother-to-child HIV transmission was assessed by the comparison of infant HIV status at 3 months and at at least one follow-up visit up to 18 months between the two groups.

Secondary efficacy variables

The effect of vitamin A on reducing HIV related symptoms was assessed by its effect on medical history and physical examination variables as well as laboratory data. HIV symptoms obtained through medical history (night sweats, fever, cough, nausea/vomiting, headaches and confusion) and physical examination (general anemia jaundice, skin, ears nose and throat, lymph nodes, respiratory examination, cardio-vascular system GIT, UG, central nervous system, and other abnormalities), T-cell counts (CD4 and CD8), and full blood counts (haemoglobin, haematocrit, erythrocytes, thrombocytes, leukocytes, lymphocytes neutophils, monocytes, eosinophils and basophils) were used to assess the efficacy of vitamin A.

2.9 Data sets analysed

The data sets analysed in this study were defined during the blind review meetings (see the minutes of the 1st and 2nd blind review meetings in Appendix 9). An Intention To Treat (ITT) and a Per-Protocol (PP) efficacy analysis was performed for the primary outcome data (infant HIV status). The safety analysis was performed on the safety population. These populations are defined below.

2.9.1 ITT Population

The ITT analysis of efficacy included all patients randomised, who received at least one dose of treatment or placebo after randomisation, with primary efficacy (HIV status of infant) data by either PCR or ELISA for at least one follow-up visit. The ITT analysis is the primary efficacy analysis.

2.9.2 PP population

The PP analysis of efficacy was based on all patients randomised who received at least one dose of treatment or placebo, with HIV results for infants based on PCR test at 3 months.

2.9.3 Safety population

All patients who took at least one dose of the study medication were analysed for safety. It was performed by treatment groups at each visit.

2.9.4 Non-compliant patients

Non-compliant patients are patients who attended one post-natal visit only (after being traced) after missing two or more consecutive visits.

2.9.5. Handling of Dropouts or missing infant HIV result

The following categories of handling dropouts or missing infant HIV test results were agreed upon at the 1st blind review meeting (see Appendix 9).

- When the PCR HIV result for an infant was missing for the 3 month visit, it was

replaced by the earliest PCR result available.

- If PCR results are missing completely they were replaced by an ELISA test at 18 months to assess the overall transmission rate.
- If a p-24 tests contradicts a PCR test, the PCR was used.
- If a PCR contradicts an ELISA on blood drawn the same day, the result was considered to be conflicting and the patient was eliminated from the ITT and PP analysis population.

2.10 Statistical methods

2.10.1 Descriptive statistics

The demographic and clinical characteristics of women and infants were summarised for both treatment groups. Some of the characteristics considered were: maternal age, HIV symptoms (as measured by medical history and physical examination) of the women and maternal full blood and T-cell counts. Full blood and T-cell counts for the infants, birth weight, length, head circumference and gender were summarised for the two treatment groups.

Continuous variables were presented using the following summary statistics: number of patients (n), mean, standard deviation (SD), minimum (min), median and maximum (max). For categorical variables frequencies and percentages for each response category were given for each treatment group.

2.10.2 Inferential statistics

Continuous variables were compared using t-tests, whereas categorical variables were compared using χ^2 -test or Fisher's exact tests. The level of statistical significance used for the comparisons in this study was 5%.

Because of the relatively large number of patients excluded from the ITT population, patients in the ITT population and those not in the ITT population per treatment group, were compared, regarding all the characteristics measured at baseline. This comparison was done to assess potential systematic differences, and therefore possible bias between patients included in the ITT population and patients excluded from the ITT population.

Baseline characteristics, as well as characteristics at each visit for both mothers and infants, were compared for Safety and ITT populations between the two treatment groups. Medical history and physical examination variables (used as indicators of HIV symptoms in this study) were compared between the two treatment groups for the ITT at each post delivery visit and for PP populations at post-delivery 3 months visit. At recruitment statistical comparisons of the two treatment groups were only done for the ITT population.

The percentages of HIV positive infants in the treatment and control groups were compared by calculating a point estimate and a 95% confidence interval for the risk difference. Furthermore, Fisher's exact test was used to compare the two treatment groups with respect to the percentages of HIV positive infants. Logistic regression

techniques were used to examine the effect of maternal vitamin A supplementation on vertical transmission controlling for CD4 and CD8 counts at baseline.

The percentage efficacy of vitamin A supplementation was defined as:

$$\frac{\text{Incidence of HIV among infants on placebo - Incidence of HIV among infants treated}}{\text{Incidence of HIV among infants on placebo}} (\%)$$

The overall transmission rates between the two groups were compared for both ITT and PP analysis populations. Early (up to 3 month) transmission rates were compared between the two groups. An estimate of the HIV transmission rate for new-born babies (up to 3 months) was obtained for this population using the placebo arm of the study.

T-cell counts and full blood counts, weight and vital signs of the two treatment groups were compared at the various time points using t -tests.

Chi-square or Fisher's exact tests were performed when comparing the percentages of patients with HIV symptoms (measured by medical history variables) and HIV related abnormalities (measured by physical examination variables) between the two groups.

Infant growth percentiles were calculated using EPIINFO version 5[81] which utilises the NCHS reference values. These percentiles were compared between the two treatment

groups. The relative risk of infant mortality between the vitamin A and placebo groups was calculated.

Secondary measurements of efficacy of vitamin A such as the reduction of HIV symptoms and HIV related abnormalities at each visit were compared between the two treatment groups for both mothers and infants.

2.10.3 Normal ranges for laboratory values for the Bloemfontein population

The normal ranges for the laboratory variables used in this study are given in Table 2.1 below. These ranges are for the Bloemfontein population, and are considered to be normal for the study participants. The patients who are considered to have abnormal laboratory characteristics are those with values less than the lower boundary of the normal range.

Table 2.1
Normal ranges used for the assessment of laboratory data[82]

Variable	Unit	Normal range	
		Lower boundary	Upper boundary
Haemoglobin	g/Dl	10.20	14.70
Haematocrit	L/L	0.32	0.47
Red blood cells	10^9 cells/litre	3.30	4.90
Eosinophils	10^9 cells/litre	0.00	0.40
Thrombocytes	10^9 cells/litre	157.00	427.00
Neutrophils	10^9 cells/litre	2.40	11.30
Lymphocytes	10^9 cells/litre	1.00	3.00
White blood cells	10^9 cells/litre	4.20	14.10
Monocytes	10^9 cells/litre	0.20	0.70
CD4	10^9 cells/litre	0.39	1.64
CD8	10^9 cells/litre	0.23	1.39
CD4/CD8 ratio		0.72	3.06

2.11 Presentation of results

The results are presented following the ICH guidelines.[83]

Chapter 3 gives an account of the study participants. A flow chart (see Figure 3.1) for patient screening and recruitment is presented, as well as the number and percentages of patients in each analysis population and number of patients per visit per treatment group (see section 3.1). Protocol violations per patient are discussed in section 3.2.

The results of the tracing process of non-attendees are presented (see section 3.3) as well as the measurements of treatment compliance (see section 3.4).

The number and percentages of patients who are in the ITT population and those not in the ITT population per treatment group, regarding all characteristics measured at baseline are presented (see section 3.5). Issues regarding consent for HIV testing and trial participation are discussed in section 3.6.

Chapter 4 presents the efficacy evaluation. The reasons for exclusion from the ITT population (efficacy analysis) are presented (see section 4.1). All baseline maternal characteristics are discussed for both Safety and ITT populations per treatment group as well as infant characteristics for the Safety population (see section 4.2). The results for pre-delivery follow-up visits (visit 2 and 3) are not given due to small numbers of patients attending those visits.

All the characteristics measured at each post-natal visit are presented for both mothers and infants (see section 4.3). Results on vitamin A efficacy are presented in section 4.4.

Chapter 5 gives the safety evaluation. Safety of vitamin A is discussed based on vital signs and laboratory values. Vital signs and the laboratory variables at 3, 6, 12 and 18 months and baseline are listed with summary statistics for each treatment. The frequencies of laboratory values (haematology) below the normal ranges are given. Adverse events and total deaths are also summarised in chapter 5.

2.12 Changes in the conduct of the study or planned analysis

2.12.1 Number of patients

It was planned to enrol a total of 400 HIV positive pregnant women over 1 year from selected antenatal clinics in Bloemfontein. However, recruitment was eventually terminated due to stringency measures applied by the Free State Health Services in the beginning of 1999. Because screening took longer than anticipated, 303 patients had been enrolled in the study over approximately 20 months by the time recruitment was stopped.

2.12.2 Administration of study medication

Originally it was planned that the registered nurse administer the medication, but due to staff shortages at the clinics the doctor (in Phase I) and the Ph.D. student (in Phase II) eventually administered the medicine.

2.12.3 Gestational age of patients

It was planned to recruit patients who were between 20 and 36 weeks pregnant but fewer patients than expected came back to collect the results of their HIV test. Therefore, patients were eventually recruited from 12 weeks gestation. Only 13 patients were recruited when the gestational age was less than 20 weeks.

2.12.4 Statistical analysis planned but not done

Survival analysis was to be used to compare the time infants were free of HIV in the treatment and control groups. Kaplan-Meier survival curves were to be used for descriptive analyses while Cox proportional hazards regression models were to be used for estimation purposes. Linear regression models were to be used to examine the effect of concurrent HIV infection or HIV exposure to serum retinol during the course of an infection.

Survival analysis could not be performed because of lack of infant PCR HIV test results over time after birth since most of the patients did not attend their follow-up visits regularly.

Most patients did not attend their follow-up visits regularly; therefore the infant HIV test result at any point post-delivery was considered for the intention to treat analysis of HIV transmission rate.

Vitamin A levels were not determined due to inadvertent discarding of samples by laboratory staff. Linear regression models, comparison of retinol concentrations between the two groups and the effect of vitamin A supplementation on the immune system could not be done due to lack of data on serum retinol.

2.12.5 Milk samples

Milk samples and blood samples at the 1 month visit were eventually not collected due to logistical problems (most mothers were not breast feeding).

2.13 Follow-up of non-attendees

Most patients missed appointment dates for study visits and had to be traced. If a phone number for a patient was available, the Ph.D. student phoned the patient as soon as an appointment was missed. However, most patients did not have telephones. From October 1998 to January 1999 a research assistant was employed specifically to follow-up non-attendees. She had to work through the backlog of non-attendees who could not be reached telephonically.

Houses and shacks are often not numbered sequentially and this numbering made it difficult for the research assistant to locate the addresses. To be more successful in following-up non-attendees, the Bloemfontein Hospice was approached to help with the follow-up of patients at their homes from February 1999. Hospice field workers know the relevant residential areas well, and were able to trace most of the non-attendees of this study.

Initially, twenty-five addresses of non-attendees were given to field workers to be followed weekly. When the address was located, information about the whereabouts of the patient was obtained (see Appendix 10). If the patient was still staying at that address she was asked to go to the clinic once for a withdrawal visit if she had missed two consecutive visits. The patient was encouraged to continue with the study if she had missed only one visit. If she did not want to continue with the study she was also withdrawn. If the baby had died, an approximate date of death and the cause were obtained, where possible.

2.14 Issues regarding consent

Issues regarding consent for HIV testing and study participation by the patients was investigated by interviewing study patients who were attending their post-natal visits from mid-July 1999 to mid-October 1999. They were asked to give consent (see Appendix 11) to participate in this investigation. Those who gave consent were interviewed by a research assistant not involved in the trial using a structured questionnaire (see Appendix 12) in Sesotho or Afrikaans.

2.15 Funding

Financial assistance for this study was received from the South African Medical Research Council (MRC) and from the University of the Free State Central Research Fund. The Foundation for Research Development (FRD) provided a bursary for Ph.D. study for the candidate.

Chapter 3: ACCOUNT OF STUDY PATIENTS

3.1 Disposition of Patients

The flowchart of patient screening and recruitment is given in Figure 3.1 below. Two thousand nine hundred and forty nine patients were counselled. Of the 2949 patients who were counselled during the screening process, 2543 patients (86.2%) were willing to have an HIV test.

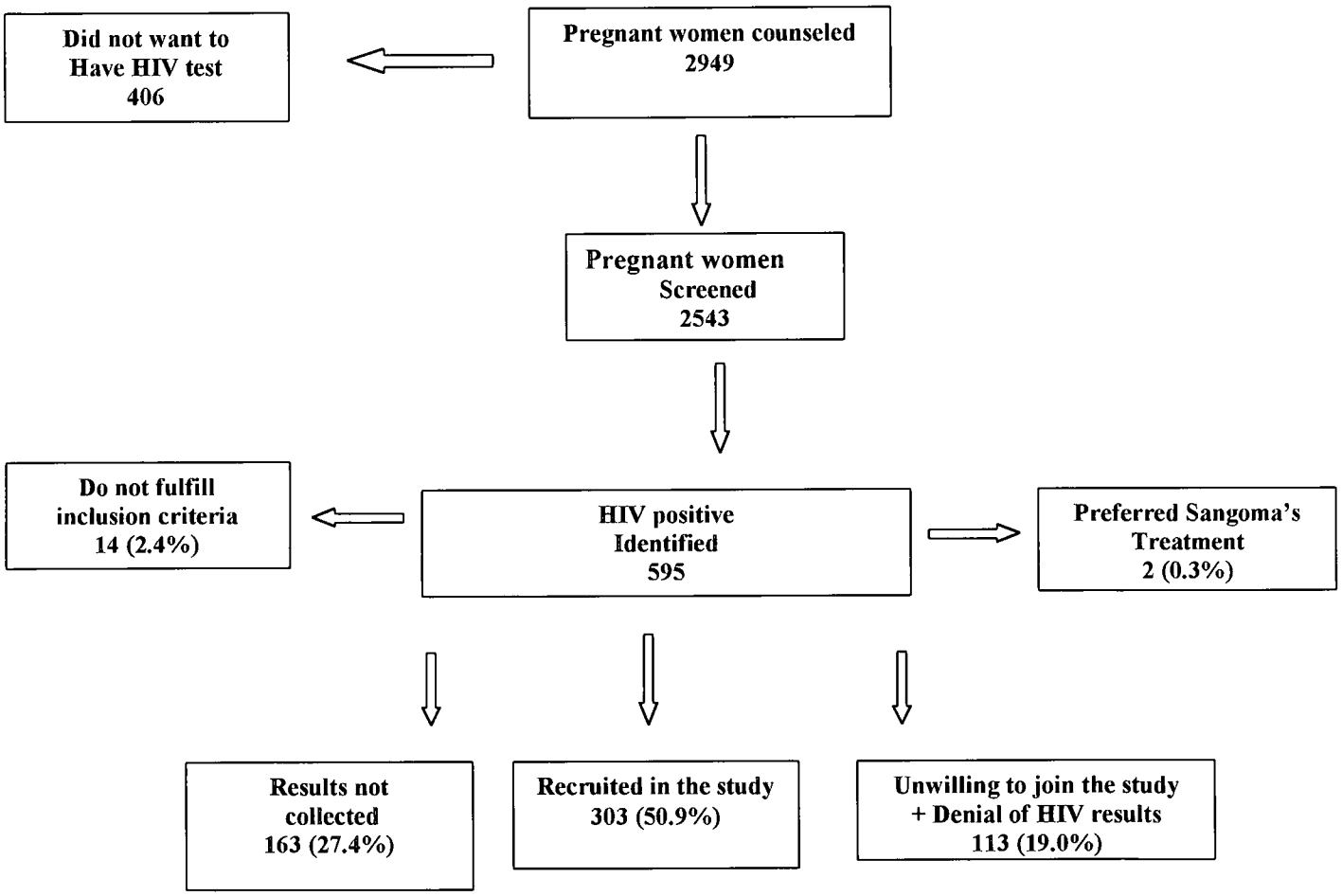

Figure 3.1 Flow chart for patient screening and recruitment

A total of 595 patients were identified as HIV positive (23.4% of those tested). Of the 595 patients identified as HIV positive, 303 patients (50.9%) were enrolled and randomised in the study, 163 patients (27.4%) did not return for their HIV test results, 2 patients (0.3%) preferred to visit a Sangoma (traditional healer) instead of participating in the study (see Figure 3.1 above), 14 patients (2.7%) did not fulfil the inclusion criteria and 113 patients (19.0%) were unwilling to participate or denied their HIV test results.

Of the 303 study participants 5 gave addresses on plots around the city of Bloemfontein. Four patients gave addresses in small towns within 160 km of Bloemfontein, were willing to participate in the study and said they would be able to come for follow-up visit. All other 294 patients gave addresses in residential areas in Bloemfontein.

Table 3.1 gives the number of patients per analysis population and the reason for exclusion from the analysis population per treatment group. Overall, about half the patients were excluded from the ITT population, and about two thirds from the PP population because many patients did not have a conclusive infant HIV result (blood sample not available, see Table 3.1 below). Table 3.1 below shows that, for both the ITT and PP analysis populations, slightly more patients were excluded from the vitamin A group than from the placebo group.

Table 3.1
Number of patients per analysis population and reasons for patients' exclusion from the analysis population
Population: All randomised patients

Reasons	Vitamin A N=152		Placebo N=151		Total N=303	
	n	%	n	%	n	%
Patients randomised	152	100.0	151	100.0	303	100.0
Patients valid for safety analysis	152	100.0	151	100.0	303	100.0
Patients valid for ITT analysis	73	48.0	85	56.3	158	52.8
Patients valid for PP analysis	50	32.9	54	35.8	104	35.0
Excluded from safety analysis						
No randomised treatment taken	0	0.0	0	0.0	0	0.0
Excluded from ITT analysis						
No conclusive HIV test result for infant	79	52.0	66	43.7	145	47.9
Excluded from PP analysis						
No conclusive HIV PCR result for infant at month three	102	67.1	97	64.2	199	65.7

The patients randomised to each treatment group, the last visit attended, reason for withdrawal and further description (where applicable) are listed in Appendix 13. The Appendix shows that many patients did not attend the follow-up visits. Of 152 patients in the vitamin A group 70 never attended a postnatal visit, similarly 57 of 151 patients in the placebo group never attended a postnatal visit. The Appendix also indicates that Hospice staff recovered information when they were tracing those patients who missed their follow-up visits. Very few patients attended the last follow-up visit (post-delivery 18 months). One of the patients in the placebo group died before delivery (see Appendix 13).

The reasons for premature termination of patients from the study per treatment group are given in Table 3.2. In both treatment groups, the majority of patients were prematurely terminated with almost 72% of patients in the vitamin A group and 68% of patients in the

placebo group. Most of the patients were lost to follow-up, nearly 58% and 46% in the vitamin A and placebo groups respectively. Few patients withdrew their consent in either group.

Table 3.2
Reasons for premature terminations
Population: All randomised patients

	Vitamin A N=152		Placebo N=151	
	n	%	n	%
Number of patients randomised	152	100.0	151	100.0
Number of patients prematurely terminated	110	72.4	102	67.5
Reasons for premature termination				
Death infants	9	5.9	17	11.3
Mothers	0	0.0	1	0.7
Non-compliance	7	4.6	8	5.3
Lost to follow-up	88	57.9	70	46.3
Consent withdrawn	6	3.9	6	4.0

The number of patients per visit, and the number of patients in the safety, ITT and PP analysis populations per treatment group are shown in Table 3.3. Only 23 patients attended pre-natal visit 3. This small number indicates that most patients were recruited in the study when their pregnancy was at a late stage. In both treatment groups most patients did not attend their follow-up visits regularly since the number of patients per visit is consistently decreasing from the 3 month post-natal visit. In both groups very few patients attended the 18 month visit. The number of patients in the placebo group for post-natal visits is slightly higher than that in the vitamin A group for all analysis populations.

Table 3.3
Number of patients at each visit by analysis population
Population: All randomised patients

		Vitamin A N=152						Placebo N =151					
		Safety		ITT		PP		Safety		ITT		PP	
		N	%	N	%	n	%	N	%	n	%	N	%
Pre-natal	Visit1	152	100.0	73	49.3	50	33.6	151	100.0	85	56.3	54	35.8
Pre-natal	Visit2	77	50.7	45	39.6	34	22.4	84	55.6	55	36.4	38	25.2
Pre-natal	Visit3	13	8.5	7	4.6	3	2.0	10	6.6	5	3.3	3	2.0
Post-natal	1month	58	38.2	50	32.9	41	27.0	58	38.4	50	33.1	37	24.5
Post-natal	3month	67	44.1	64	42.1	50	32.9	74	49.0	74	49.7	54	35.8
Post-natal	6month	59	38.8	57	37.5	43	28.3	71	47.0	70	46.4	47	31.1
Post-natal	9month	57	37.5	56	36.8	41	27.0	64	42.4	63	41.7	41	27.2
Post-natal	12month	51	33.5	51	33.6	37	24.3	63	41.7	63	41.7	40	26.5
Post-natal	15month	49	32.2	48	31.6	34	22.4	56	37.1	57	37.7	39	25.8
Post-natal	18month	42	27.6	41	27.0	30	19.7	49	32.5	49	32.5	34	22.5

3.2 Patient protocol violations

Protocol violations (see Appendix 14) were listed per patient describing the nature of the violation. A major violation occurs when a patient did not attend the clinic visits regularly such that her infant does not have any HIV results. Therefore patients who did not attend any post delivery visit after the baby was one month old committed major violations of the protocol. A minor violation occurs when a patient did not attend her clinic visits regularly but had at least one HIV test result for the infant. The results in Table 3.3 above show that the majority of patients violated the protocol at the post-delivery visits in both treatment groups.

3.3 Tracing of patients who absconded their visits

This section describes the tracing process of non-attendees. Of 303 study participants 134 (44.2%) gave addresses reflecting formal houses and 169 (55.8%) had addresses reflecting informal housing. Table 3.4 shows the number of patients who missed a particular type of visit and the tracing of the woman's address. The results in Table 3.4 show that a total of 191 (63% of all the participants) missed one or more visits and had to be traced. The majority (140, 73%) of the non-attendees missed appointments in the postnatal phase. Of the 140 patients who missed visits after delivery, 107 (76%) missed the first post-natal visit (when baby was one month old). Of 191 non-attendees about 18% had given a non-existing address (address that could not be found). Of the addresses that could be found, the woman was not known or no longer stayed at the address in about 48%. A new address could be found for the woman in only 12 cases (15.8%) of those who moved or were not known at that address.

Table 3.4

Extent of non-attendance and the tracing process

Extend	Number (%)
Total traced	**191**
Traced during antenatal phase	51 (26.7)
Traced during postnatal phase	140 (73.3)
Non-existing addresses given	34 (17.8)
Addresses that could be found	157 (82.2)
Traced in postnatal phase	**140**
Missed visit when baby was one month old	107 (76.4)
Missed visit when the baby was three months or more	33 (23.6)
Addresses that could be found	**157**
Woman still at the address	81 (51.6)
Woman moved or not known at that address	76 (48.4)
Woman's new address obtained	12/76 (15.8)

About 25% of the 191 non-attendees were visited more than once in order to obtain information on the patient's whereabouts.

Table 3.5 shows the final results of the tracing process. Sixty-six (34.6%) of non-attendees where seen at the clinic by the end of June 2000 and 51 of those patients continued with the trial. Fifteen patients were prematurely withdrawn since they had missed two or more consecutive visits or no longer wanted to continue. Fifteen babies and one mother had died. Twenty women promised to come to the clinic but never came. Eighty-nine women could not be traced because the address does not exist, no such woman stayed at that address or women moved and new address was unknown. Of the 51 patients continuing with the trial, 16 had to be traced at a later stage again.

Table 3.5
Overall tracing results (N=191)

Category	Number (%)
Traced and came to the clinic	66 (34.6)
Continued with study	51
Withdrawn	15
Traced and baby had died	15 (7.8)
Non-existing address or woman not known at that address	48 (25.1)
Woman moved and could not be traced	41 (21.5)
Traced but did not come to the clinic	20 (10.5)
Woman died	1 (0.5)

Reasons given for not attending the clinic on their appointment dates are given in Table 3.6. Only 98 cases (51.3%) of 191 traced patients could give a reason for not attending the visit. Of the 98 patients, 45 (45.9%) could not attend their clinic visit because the baby had died or the patient was no longer interested in the trial or the patient was now

working so she did not have time to go to the clinic. More than 50% of 98 patients gave unclear reasons, such as 'I forgot', 'no reason', 'lost appointment card', 'no appointment given' or 'no money'.

Table 3.6
Reasons for missing the visit appointment (N=98)

Reasons for missing visit that could be obtained	Number (%)
Could not come because baby had died	15 (15.3)
No longer interested	18 (18.4)
Patient got a job so no time	12 (12.2)
Patient was sick/no money	16 (16.3)
No appointment given/lost appointment card	20 (20.4)
No clear reason/ forgot	17 (17.3)

3.4 Measurements of treatment compliance

During phase I of the study, patients were given diaries to tick each day on which they took the tablets. Appendix 15 shows the data for patients who brought back the diaries and the period they took the tablets. However, most patients did not return the diaries; they either lost them or simply said they had forgotten them at home. Only 65 (21.5%) of the 303 study participants returned the diary with 36 in the vitamin A group and 29 in the placebo group. Of the 65 patients who returned the diaries 10 did not take the tablets consecutively as expected and one diary was spoilt. Two of these 10 claimed that they took the tablets every day although they did not indicate on the diary. The patients always

brought back the packets of tablets, which were either empty or had very few tablets left. Patients generally claimed that they were taking the tablets every day although they had forgotten the diaries. In phase II of the study (post-delivery) compliance was assured in the patients that attended the respective visits, because the medication was administered to the patients by the Ph.D. student at the clinic.

3.5 Comparison of patients in the ITT population and those who are not

The relatively high proportion of patients excluded from the ITT population (primary analysis population) warrants this section comparing patients who were included in the ITT population with those who were not. Characteristics measured at recruitment are compared. This comparison is done in order to assess whether there are any systematic differences between patients included in the ITT population and those who were not included; any such differences could bias the study results because of the many patients that were excluded from the analysis.

3.5.1 Demographic data

Table 3.7 compares the home language and race of patients who respectively are in the ITT population and those who are not. The percentages for these demographic characteristics are similar and there is no statistically significant difference in home language and race between patients in the ITT population and those who are not, in either treatment group.

Table 3.7
Home language and race: ITT vs non-ITT population
Population: All randomised patients

Treatment	Variable	Characteristic	Not in ITT		ITT		P-value
			n	%	n	%	
				N=79		N=73	
Vitamin A	Race	White	0	0.0	1	1.4	
		Black	74	93.7	66	90.4	0.5186
		Coloured	5	6.3	6	8.2	
	Home			N=79		N=73	
	Language	Afrikaans	6	7.6	6	8.2	
		English	0	0.0	0	0.0	
		Sotho	53	67.1	50	68.5	0.9886
		Tswana	10	12.7	8	11.0	
		Xhosa	10	12.6	9	12.3	
				N=65		N=85	
Placebo	Race	White	0	0.0	0	0.0	
		Black	64	98.5	81	95.3	0.2842
		Coloured	1	1.5	4	4.7	
				N=64		N=85	
	Home						
	Language	Afrikaans	2	3.1	6	7.1	
		English	0	0.0	1	1.2	
		Sotho	48	75.0	55	64.7	0.1814
		Tswana	4	6.2	14	16.5	
		Xhosa	10	15.6	9	10.6	

The age, height, weight and gestational period of patients, who respectively are in the ITT population and those who are not, are compared in Table 3.8. The means of these demographic characteristics are similar for patients in the ITT population and those who are not, in both treatment groups. There is no statistically significant difference in any of these variables between patients in ITT population and those who are not, in either treatment group.

Table 3.8
Demographic data at Recruitment: ITT vs non-ITT population
Population: All randomised patients

Treatment	Variable[unit]	Statistic	Not in ITT	ITT	P-value
Vitamin A	Age [years]	N	79	73	
		Mean	26.3	25.8	0.6087
		SD	5.0	5.7	
		Min	16.0	16.0	
		Median	25.0	24.0	
		Max	37.0	39.0	
	Height [cm]	N	75	70	
		Mean	158.6	158.4	0.8995
		SD	7.8	6.4	
		Min	145.0	143.0	
		Median	158.0	159.0	
		Max	182.0	174.0	
	Weight [kg]	N	77	71	
		Mean	66.5	65.7	0.7141
		SD	12.4	12.7	
		Min	44.0	41.0	
		Median	64.0	63.0	
		Max	93.0	105.0	
	Gestational age[weeks]	N	79	73	
		Mean	27.9	26.6	0.1172
		SD	4.5	5.1	
		Min	16.0	12.0	
		Median	28.0	26.0	
		Max	36.0	36.0	
Placebo	Age [years]	N	66	85	
		Mean	26.6	26.4	0.7956
		SD	5.1	4.8	
		Min	16.0	17.0	
		Median	27.0	26.0	
		Max	39.0	42.0	
	Height [cm]	N	64	81	
		Mean	156.7	156.9	0.8561
		SD	6.5	7.1	
		Min	145.0	143.0	
		Median	156.0	157.0	
		Max	177.0	178.0	
	Weight [kg]	N	65	82	
		Mean	64.7	64.4	0.8868
		SD	12.6	12.6	
		Min	39.0	42.5	
		Median	63.0	62.0	
		Max	98.0	105.0	
	Gestational age [weeks]	N	66	83	
		Mean	28.0	27.4	0.3756
		SD	4.7	3.7	
		Min	17.0	17.0	
		Median	29.0	27.0	
		Max	36.0	36.0	

3.5.2 Medical history

The percentage of patients with HIV symptoms at recruitment for patients in the ITT population and those who are not are compared in Table 3.9. These percentages are similar for patients in the ITT population and those who are not, in both treatment groups. There is no statistically significant difference in any of the symptoms between the patients in the ITT population and those who are not in ITT population in either treatment group. However, in the placebo group the percentage with night sweats (10.6%) was higher for those patients who are not in the ITT population than that (3.6%) of patients in the ITT population.

Table 3.9
HIV symptoms on medical history at Recruitment: ITT vs non-ITT population
Population: All Randomised patients

Treatment	Variable	Not in ITT		ITT		P-value
		n	%	n	%	
			N=79		N=73	
Vitamin A	Night sweats	13	16.7	11	14.9	0.8147
	Coughing	14	17.9	19	25.7	0.2146
					N=71	0.9153
	Fever	15	19.2	13	18.1	
					N=72	0.8669
	Nausea/Vomiting	6	7.7	6	8.2	
	Headache	28	35.9	24	32.4	0.7390
			N=65		N=65	0.5591
	Confusion	1	1.6	2	3.0	
			N=66		N=84	
Placebo	Night sweats	7	10.6	3	3.6	0.0864
	Coughing	12	18.2	18	21.4	0.6217
	Fever	8	12.1	13	15.5	0.5567
					N=83	0.7771
	Nausea/Vomiting	4	6.1	6	7.2	
			N=65		N=83	0.4926
	Headache	20	30.8	20	36.1	
			N=57		N=76	0.7694
	Confusion	2	3.5	2	2.6	

3.5.3 Vital signs

Table 3.10 compares the vital signs of the patients in the ITT population and those who are not. The vital signs and percentages of patients with hypertension for patients in the ITT population are similar to those who are not. There is no statistically significant

difference in any of the vital signs between those patients in ITT population and those who are not, except for systolic blood pressure in the placebo group with a p-value of 0.0272. However the difference (112.9 vs 109.1) is not clinically significant.

Table 3.10
Vital signs at Recruitment: ITT vs non-ITT population
Population: All randomised patients

Treatment	Variable[unit]	Statistic	Not in ITT	ITT	P-value
Vitamin A	Systolic blood pressure[mmHg]	N	79	73	
		Mean	113.1	112.2	0.6858
		SD	13.3	11.4	
		Min	80.0	90.0	
		Median	110.0	110.0	
		Max	150.0	145.0	
	Diastolic blood pressure[mmHg]	N	79	73	
		Mean	67.0	64.0	0.1205
		SD	12.5	11.2	
		Min	40.0	40.0	
		Median	70.0	60.0	
		Max	96.0	90.0	
	Hypertension	n/N	6/79	1/73	
		%	7.6	1.3	0.0673
	Heart rate[beats/min]	N	72	69	
		Mean	74.6	76.4	0.2567
		SD	7.8	10.6	
		Min	58.0	58.0	
		Median	76.0	74.0	
		Max	98.0	120.0	
Placebo	Systolic blood pressure[mmHg]	N	66	84	
		Mean	112.9	109.1	0.0272
		SD	9.6	11.0	
		Min	90.0	90.0	
		Median	110.0	110.0	
		Max	140.0	150.0	
	Diastolic blood pressure[mmHg]	N	66	84	
		Mean	63.0	63.2	0.9161
		SD	11.4	11.2	
		Min	40.0	40.0	
		Median	60.0	60.0	
		Max	80.0	90.0	
	Hypertension	n/N	2/66	1/84	
		%	3.0	1.2	0.4243
	Heart rate[beats/min]	N	59	76	
		Mean	73.8	76.3	0.1015
		SD	8.5	8.8	
		Min	58.0	58.0	
		Median	72.0	76.0	
		Max	102.0	100.0	

3.5.4 Physical examination

Table 3.11 compares the abnormalities found during physical examination between the patients in the ITT population and those who are not. The percentages of patients with abnormalities in the ITT and non-ITT populations are similar except for skin in both treatment groups and lymph nodes in the placebo group. However, there is no statistically significant difference regarding any category of abnormalities between patients in the ITT population and those who are not.

Table 3.11
Abnormalities on physical examination at Recruitment: ITT vs non-ITT population
Population: All randomised patients

Treatment	Variable	Not in ITT		ITT		P-value
		n	%	n	%	
			N=79		N=73	
Vitamin A	Anaemia /Jaundice	4	5.1	8	11.0	0.1781
	Lymphadenopathy	8	10.1	10	13.7	0.4959
	Cardio-Vascular System (CVS)	2	2.5	2	2.7	0.9362
	Gastro-Intestinal Tract (GIT)	1	1.3	2	2.7	0.5140
	Unitary Gut (UG)	5	6.5	7	10.0	0.4082
	Central Nervous System (CNS)	0	0.0	1	1.4	0.2966
	Ear, Nose and Throat (ENT)	8	10.1	8	11.0	0.8673
	Skin	10	12.7	4	5.5	0.1262
	Respiratory	4	5.1	4	5.5	0.9086
			N=66		N=84	
Placebo	Anaemia /Jaundice	4	6.1	7	8.3	0.5961
	Lymphadenopathy	6	9.1	14	16.7	0.1755
	Cardio-Vascular System (CVS)	2	3.0	2	2.4	0.8064
	Gastro-Intestinal Tract (GIT)	0	0.0	0	0.0	0.3738
					N=80	0.9944
	Unitary Gut (UG)	5	7.6	6	7.5	
	Central Nervous System (CNS)	0	0.0	0	0.0	
					N=82	0.7518
	Ear, Nose and Throat (ENT)	4	6.1	4	4.9	
	Skin	2	3.0	8	9.5	0.1135
	Respiratory	0	0.0	0	0.0	

3.5.5 Obstetrical data

Table 3.12 compares gravity, parity and trimester for the patients in the ITT population and those who are not. The majority of patients were recruited when they were in the 3rd trimester in both groups for both ITT and non-ITT populations. Most patients had a

gravity of 2 or more. There is no statistically significant difference in gravity, parity and trimester between the patients in the ITT population and those who are not, in either treatment group. However, the difference in gestational age in the placebo group is almost statistically significant (with p=0.0513).

Table 3.12
Obstetrical status at Recruitment: ITT vs non-ITT population
Population: All randomised patients

Treatment	Characteristic		Not in ITT		ITT		P-value
			N	%	n	%	
				N=79		N=73	
Vitamin A	Gestational age	1st trimester	0	0.0	1	1.4	
		2nd trimester	5	6.3	7	9.6	0.4313
		3rd trimester	74	93.7	65	89.0	
				N=78		N=73	
	Parity	P(0)	30	38.5	32	43.8	
		P(1)	31	39.7	29	39.7	0.6608
		P(2 or more)	17	21.8	12	16.4	
				N=78		N=73	
	Gravity	G(1)	29	37.2	32	43.8	0.2524
		G(2 or more)	49	62.8	41	56.2	
				N=66		N=85	
Placebo	Gestational age	1st trimester	0	0.0	2	2.4	
		2nd trimester	7	10.6	2	2.4	0.0513
		3rd trimester	59	89.4	81	95.3	
				N=64		N=83	
	Parity	P(0)	19	29.7	29	34.9	
		P(1)	25	39.1	36	43.4	0.4178
		P(2 or more)	20	31.3	18	21.7	
				N=64		N=83	
	Gravity	G(1)	19	29.7	28	33.7	0.6019
		G(2 or more)	45	70.3	55	66.3	

3.5.6 Laboratory data

Full blood counts for the patients in the ITT population and those who are not are compared in Table 3.13. For both treatment groups, the means of the full blood counts are similar for patients in the ITT population and those who are not. There is no statistically significant difference in any of these variables between patients in the ITT population and those who are not except for lymphocytes in the placebo group (with p=0.0437). However the difference (1.63 vs 1.82) is not clinically significant.

Table 3.13
Full blood counts at Recruitment: ITT vs non-ITT population
Population: All randomised patients

Treatment	Variable[unit]	Statistic	Not in ITT	ITT	P-value
Vitamin A	Haemoglobin [g/dl]	N	79	72	
		Mean	10.93	11.17	0.2451
		SD	1.20	1.31	
		Min	8.10	8.10	
		Median	10.90	11.25	
		Max	13.60	14.10	
	Haematocrit [L/L]	N	79	72	
		Mean	0.333	0.340	0.1956
		SD	0.033	0.037	
		Min	0.260	0.260	
		Median	0.340	0.340	
		Max	0.400	0.420	
	Red blood cells [10^9 cells/litre]	N	79	71	
		Mean	3.751	3.768	0.7926
		SD	0.376	0.433	
		Min	2.700	3.070	
		Median	3.700	3.700	
		Max	5.270	4.710	
	White blood cells [10^9 cells/litre]	N	79	71	
		Mean	6.86	6.70	0.6278
		SD	2.13	1.91	
		Min	3.10	3.20	
		Median	6.50	6.70	
		Max	13.60	13.60	
	Lymphocytes [10^9 cells/litre]	N	79	72	
		Mean	1.81	1.72	0.3772
		SD	0.68	0.53	
		Min	0.71	0.40	
		Median	1.70	1.75	
		Max	4.20	3.80	
	Neutrophils [10^9 cells/litre]	N	79	72	
		Mean	4.50	4.32	0.5073
		SD	1.66	1.51	
		Min	2.00	1.60	
		Median	4.20	4.18	
		Max	9.30	8.02	
	Monocytes [10^9 cells/litre]	N	79	72	
		Mean	0.369	0.386	0.4760
		SD	0.141	0.153	
		Min	0.170	0.100	
		Median	0.360	0.380	
		Max	1.010	1.090	
	Eosinophils [10^9 cells/litre]	N	79	71	
		Mean	0.125	0.151	0.2297
		SD	0.099	0.641	
		Min	0.000	0.000	
		Median	0.100	0.100	
		Max	0.500	1.010	
	Thrombocytes [10^9 cells/litre]	N	79	72	
		Mean	262.4	267.8	0.6724
		SD	83.4	69.5	
		Min	100.0	125.0	
		Median	249.0	256.0	
		Max	543.0	496.0	

Treatment	Variable[unit]	Statistic	Not in ITT	ITT	P-value
Placebo	Haemoglobin[g/dl]	N	63	83	
		Mean	11.01	11.00	0.9603
		SD	1.38	1.30	
		Min	7.50	5.80	
		Median	11.20	11.10	
		Max	14.20	16.20	
	Haematocrit [L/L]	N	63	83	
		Mean	0.334	0.337	0.6314
		SD	0.039	0.356	
		Min	0.230	0.210	
		Median	0.340	0.340	
		Max	0.420	0.480	
	Red blood cells [10^9 cells/litre]	N	63	83	
		Mean	3.776	3.775	0.9901
		SD	0.367	0.375	
		Min	2.880	2.850	
		Median	3.750	3.790	
		Max	4.600	5.200	
	White blood cells [10^9 cells/litre]	N	63	83	
		Mean	6.54	6.94	0.1946
		SD	1.95	1.74	
		Min	2.70	3.20	
		Median	6.20	6.80	
		Max	11.50	11.70	
	Lymphocytes [10^9 cells/litre]	N	63	83	
		Mean	1.63	1.82	0.0437
		SD	0.48	0.64	
		Min	0.80	0.70	
		Median	1.59	1.80	
		Max	3.50	4.60	
	Neutrophils [10^9 cells/litre]	N	63	83	
		Mean	4.38	4.58	0.4244
		SD	1.64	1.46	
		Min	1.10	2.00	
		Median	4.20	4.50	
		Max	9.80	9.00	
	Monocytes [10^9 cells/litre]	N	63	83	
		Mean	0.355	0.367	0.6510
		SD	0.154	0.146	
		Min	0.100	0.090	
		Median	0.300	0.320	
		Max	0.960	0.840	
	Eosinophils [10^9 cells/litre]	N	62	83	
		Mean	0.132	0.129	0.8903
		SD	0.130	0.127	
		Min	0.000	0.000	
		Median	0.100	0.010	
		Max	0.600	0.630	
	Thrombocytes [10^9 cells/litre]	N	63	83	
		Mean	278.8	267.8	0.3569
		SD	75.0	62.8	
		Min	130.0	134.0	
		Median	279.0	262.0	
		Max	462.0	476.0	

Table 3.14 compares the T-cell counts for patients in the ITT population and those who are not. The means of the T-cell counts for patients who are not in the ITT population are almost equal to those for patients in the ITT population for both treatment groups. There

is no statistically significant difference in T-cell counts for patients in the ITT population and those who are not for either treatment group.

Table 3.14
T-cell counts at Recruitment: ITT vs non-ITT population
Population: All randomised patients

Treatment	Variable[unit]	Statistic	Not in ITT	ITT	P-value
Vitamin A	CD4 counts [10^9 cells/litre]	N	79	71	
		Mean	0.433	0.435	0.9584
		SD	0.226	0.191	
		Min	0.020	0.090	
		Median	0.420	0.430	
		Max	1.260	0.960	
	CD8 counts [10^9 cells/litre]	N	79	71	
		Mean	0.87	0.89	0.7113
		SD	0.42	0.37	
		Min	0.20	0.14	
		Median	0.85	0.84	
		Max	2.58	2.25	
	CD4/CD8 ratio	N	79	71	
		Mean	0.567	0.542	0.6427
		SD	0.344	0.292	
		Min	0.030	0.090	
		Median	0.470	0.460	
		Max	1.830	1.440	
Placebo	CD4 counts [10^9 cells/litre]	N	65	83	
		Mean	0.429	0.459	0.3489
		SD	0.194	0.198	
		Min	0.090	0.050	
		Median	0.400	0.450	
		Max	0.970	1.090	
	CD8 counts [10^9 cells/litre]	N	65	83	
		Mean	0.80	0.88	0.2096
		SD	0.40	0.33	
		Min	0.33	0.25	
		Median	0.79	0.82	
		Max	2.30	2.43	
	CD4/CD8 ratio	N	65	83	
		Mean	0.614	0.586	0.6185
		SD	0.371	0.324	
		Min	0.140	0.050	
		Median	0.520	0.510	
		Max	1.840	2.000	

Table 3.15 shows the percentages of patients with laboratory values less than the lower boundary of the normal range (see Table 2.1). The highest percentage of patients with abnormal values in both treatment groups was for haematocrit, followed by haemoglobin and red blood cells for vitamin A group and monocytes for placebo group.

Table 3.15
Abnormally low Full blood counts at Recruitment
Population: All randomised patients

Variable	Lower boundary Of normal range	Vitamin A N=151 n	%	Placebo N=146 n	%
Haemoglobin	10.20	37	24.5	32	21.9
Haematocrit	0.32	43	28.5	35	24.0
			N=150		
Red blood cells	3.30	17	11.3	9	6.2
			N=150		
White blood cells	4.20	8	5.3	5	3.4
Lymphocytes	1.00	8	5.3	8	5.5
Neutrophils	2.40	9	6.0	5	3.4
Monocytes	0.20	6	4.0	11	7.5
			N=150		N=145
Eosinophils	0.00	0	0.0	0	0.0
Thrombocytes	157.0	5	3.3	6	4.1

The percentages of patients in the ITT population and those who are not, with full blood counts values lower than the lower boundary of the normal range are compared in Table 3.16. There is no statistically significant difference in the percentages of any variable between the patients in the ITT population and those who are not for both groups.

Table 3.16
Abnormally low Full blood counts at Recruitment: ITT vs non-ITT population
Population: All randomised patients

Treatment	Variable	Lower boundary Of normal range	Not in ITT n	%	ITT n	%	P-value
				N=79		N=72	
Vitamin A	Haemoglobin	10.20	20	25.3	17	23.6	0.8077
	Haematocrit	0.32	22	27.9	21	29.2	0.8577
	Red blood cells	3.30	6	7.6	11	15.5	0.1276
						N=71	0.3772
	White blood cells	4.20	3	3.8	5	7.0	
	Lymphocytes	1.00	5	6.3	3	4.2	0.5535
	Neutrophils	2.40	4	5.1	5	6.9	0.6258
	Monocytes	0.20	3	3.8	3	4.2	0.9077
						N=71	
	Eosinophils	0.00	0	0.0	0	0.0	
	Thrombocytes	157.0	3	3.8	2	2.8	0.7265
				N=63		N=83	
Placebo	Haemoglobin	10.20	15	23.8	17	20.5	0.6302
	Haematocrit	0.32	17	27.0	18	21.7	0.4577
	Red blood cells	3.30	4	6.4	5	6.0	0.9355
	White blood cells	4.20	4	6.4	1	1.2	0.0905
	Lymphocytes	1.00	4	6.4	4	4.8	0.6874
	Neutrophils	2.40	4	6.4	1	1.2	0.0905
	Monocytes	0.20	6	9.5	5	6.0	0.4275
				N=62			
	Eosinophils	0.00	0	0.0	0	0.0	
	Thrombocytes	157.0	4	6.4	2	2.4	0.2350

The percentages of the patients with the T-cell counts less than the lower boundary of the normal range are given in Table 3.17. Nearly 14% and 8% of patients had CD4 counts below 0.20 (indicative of AIDS) at recruitment in the vitamin A and placebo groups respectively. Most patients had CD4/CD8 ratios lower than the normal range in the two treatment groups. The percentage of patients with RPR positive result in vitamin A was slightly higher than that of placebo group.

Table 3.17
Abnormally low T-cell counts and RPR at Recruitment:
Population: All randomised patients

Variable	Lower boundary Of normal range	Vitamin A N=150 n	%	Placebo N=148 n	%
CD4 counts	0.200	21	14.0	12	8.1
CD4 counts	0.390	64	42.7	59	39.9
CD8 counts	0.230	3	2.0	0	0.0
CD4/CD8 ratio	0.720	107	71.3	116	78.4
			N=136		N=132
RPR	Positive	47	34.6	42	31.8

Table 3.18 compares the percentages of the patients with T-cell counts less than the lower limit of the normal range for patients in the ITT population and those who are not. In the vitamin A group more than 10% of patients in ITT and non-ITT populations had CD4 below 0.20 (criteria for diagnosis of AIDS) at recruitment. There is no statistically significant difference in any of the percentages of the T-cell counts between patients in the ITT population and those who are not.

Table 3.18
Abnormally low T-cell counts and RPR at Recruitment: ITT vs non-ITT population
Population: All randomised patients

Treatment	Variable	Lower boundary of normal	Not in ITT		ITT		P-value
			n	%	n	%	
				N=79		N=71	
Vitamin A	CD4 counts	0.200	10	12.7	11	15.5	0.6174
	CD4 counts	0.390	36	45.6	28	39.4	0.4483
	CD8 counts	0.230	2	2.5	1	1.4	0.6237
	CD4/CD8 ratio	0.720	55	69.6	52	73.2	0.6246
				N=74		N=62	
	RPR	Positive	27	36.5	20	32.3	0.6056
				N=65		N=83	
Placebo	CD4 counts	0.200	7	10.8	5	6.0	0.2939
	CD4 counts	0.390	29	44.6	30	36.1	0.2962
	CD8 counts	0.230	0	0.0	0	0.0	
	CD4/CD8 ratio	0.720	53	81.5	63	75.9	0.4086
				N=60		N=72	
	RPR	Positive	16	26.7	26	36.1	0.2460

3.6 Issues regarding consent for HIV testing and study participation

This section describes the results obtained when investigating the quality of counselling given to the patients and participants' level of understanding of the consent they gave for HIV testing and trial participation. Table 3.19 shows the results on participants' perception regarding HIV testing and trial participation (also see Appendix 1). Of the 92 participants interviewed, 86 (94.6%) indicated that they were counselled for HIV testing and 95.3% of the 86 participants stated that they understood counselling. Only 1.1% of 91 participants indicated that they did not give consent for HIV testing. About 3.3% stated that they felt obliged to take part in the study. Only 24.2% felt that they could withdraw at any time and 92.3 % stated that they thought they would no longer get good medical care if they withdrew from the trial.

Table 3.19
Participants' perception regarding HIV testing and trial participation

Category	%Yes	%No	%Unsure
Was counselling given to you before HIV testing (N=92)	94.6	5.4	0.0
Did you understand counselling (N=86)	95.3	3.5	1.2
Did you give consent for HIV testing (N=91)	98.9	1.1	0.0
Did you want to participate in the trial (N=91)	98.9	1.1	0.0
Did you feel forced to participate in the trial (N=91)	3.3	96.7	0.0
Can you withdraw from the trail any time (N=91)	24.2	73.6	2.2
Do you feel that you no longer get good medical care if to withdraw from the trial (N=91)	92.3	7.7	0.0

Table 3.20 shows the level of knowledge of follow-up. Of the 92 participants only 30.4% knew that they must attend follow-up visit until the infant is 18 month old. Nearly 32% of the 92 participants were unsure as to how long they must come for follow-up. About 10% of the 92 participants stated that they were not told, or until the doctor told them to stop.

Table 3.20
Knowledge of length of follow-up

Till when post-natal visit must continue N=92	%
Infant is 18 months old	30.4
Unsure	33.7
Have not been told	9.8
Until doctor says I must stop	9.8
Other incorrect answers	16.3

3.7 Summary: Study patients

Of 2543 patients who were screened 23.4% were identified as HIV positive. About 51% of 595 HIV positive patients were recruited in the study. In total 152 patients were randomly allocated to vitamin A group and 151 to placebo group. A total of 158 patients were lost to follow-up. Only 91 patients attended the last follow-up visit (when the baby was 18 months old). A total of 26 babies and one mother died during the study.

Most of non-attendance occurred between the antenatal and post-natal phase. Nearly 73% (140 patients) of non-attendees in this study missed visits in the postnatal phase. Eighty nine cases of non-attendees (191) could not be traced because the given address does not exist, no such woman stayed at that address or woman moved and the new address is unknown.

One hundred and fifty eight patients had a conclusive infant HIV test result (patients in ITT analysis population) and 104 patients had a conclusive infant HIV test result when the baby was 3 months old (patients in per protocol analysis population). Generally there were no statistically significant differences in baseline demographic data, medical history, vital signs, physical examination, obstetrical and laboratory data between patients in ITT population and those not in ITT population.

About 95% of the 92 study participants indicated that they were counselled and gave consent for HIV testing. Only 3.3% of the 92 participants stated that they felt forced into taking part in the trial.

Chapter 4: EFFICACY EVALUATION

4.1 Reasons for exclusion from efficacy analysis

Patients excluded from the efficacy analysis in each treatment group and the reasons for exclusion are listed in Appendix 14 with a summary in chapter 3 (see Table 3.1). In both treatment groups, the majority of patients were excluded because they did not attend postnatal visits so that no blood could be drawn from the infants for the HIV test. A more detailed summary of the reasons for exclusion from the efficacy analysis (ITT population) is presented in Table 4.1 below. Overall, nearly 48% of the study participants were excluded from the ITT efficacy analysis. Most of these never attended any post-delivery visit, or the infant died before blood was drawn. Two patients had conflicting infant HIV test results.

Table 4.1
Reasons for exclusion from ITT analysis (No HIV test result for infant)
Population: All randomised patients

Reasons for exclusion from ITT	Vitamin A N=152		Placebo N=151	
	n	%	n	%
Patients randomised	152	100.0	151	100.0
Patients included in ITT	73	48.0	85	56.3
Reasons (No infant HIV test result)				
Never attended post-delivery visit	66	43.4	50	33.1
Baby died before blood is drawn	7	4.6	11	7.3
Conflicting infant HIV result	2	1.3	0	0.0
No blood drawn from infant	4	2.6	4	2.6
Mother died before delivery	0	0.0	1	0.7

4.2 Comparison of baseline characteristics

Results of the comparison of patients in Vitamin A and placebo groups are given for the Safety and ITT population for all baseline characteristics of the mothers. The infants are compared for the Safety population analysis because the number of infants in the Safety and ITT populations are almost equal.

4.2.1 Demographic variables

Home language and race per treatment group are shown in Table 4.2. Most of the patients who participated in this study were black, namely nearly 92% in the vitamin A group and 97% in the placebo group in the safety population. The majority (almost 70%) of study participants were Sotho speaking women, followed by Xhosa and Tswana with about

12% of patients each in both treatment groups in the Safety population. There is no statistically significant difference regarding home language or race between the patients in vitamin A and those in placebo group for the ITT population.

Table 4.2
Home language and race: Mothers
Population: Safety/ITT

Population	Variable	Characteristic	Vitamin A		Placebo		
			n	%	n	%	
Safety				N=152		N=150	
	Race	White	1	0.7	0	0.0	
		Black	140	92.1	145	96.7	
		Coloured	11	7.2	5	3.3	
	Home Language			N=152		N=149	
		Afrikaans	12	7.9	8	5.4	
		English	0	0.0	1	0.7	
		Sotho	103	67.8	103	69.1	
		Tswana	18	11.8	18	12.1	
		Xhosa	19	12.5	19	12.7	
ITT				N=73		N=85	
	Race	White	1	1.4	0	0.0	
		Black	66	90.4	81	95.3	P=0.3622
		Coloured	6	8.2	4	4.7	
	Home Language						
		Afrikaans	6	8.2	6	7.1	
		English	0	0.0	1	1.2	
		Sotho	50	68.5	55	64.7	P=0.7405
		Tswana	8	11.0	14	16.5	
		Xhosa	9	12.3	9	10.6	

The age, height, weight and gestational period of patients are shown in Table 4.3. At recruitment, the patients were about 26 years old on average, in both treatment groups. The mean duration of pregnancy for patients at recruitment was about 27 weeks for both treatment groups. There is no statistically significant difference in any of these variables between patients in vitamin A group and those in placebo group for the ITT population.

Table 4.3
Demographic data at Recruitment: Mothers
Population: Safety/ITT

Population	Variable[unit]	Statistic	Vitamin A	Placebo	
Safety	Age [years]	N	152	151	
		Mean	26.1	26.5	
		SD	5.3	4.9	
		Min	16.0	16.0	
		Median	25.0	26.0	
		Max	39.0	42.0	
	Height [cm]	N	145	145	
		Mean	158.5	156.8	
		SD	6.8	6.8	
		Min	143.0	143.0	
		Median	158.0	156.0	
		Max	182.0	178.0	
	Weight [kg]	N	148	147	
		Mean	66.1	64.6	
		SD	12.5	12.6	
		Min	41.0	39.0	
		Median	63.7	62.5	
		Max	104.0	105.0	
	Gestation [weeks]	N	152	149	
		Mean	27.3	27.7	
		SD	4.8	4.1	
		Min	12.0	17.0	
		Median	27.5	28.0	
		Max	36.0	36.0	
ITT	Age [years]	N	73	85	
		Mean	25.8	26.4	P=0.4792
		SD	5.7	4.8	
		Min	16.0	17.0	
		Median	24.0	26.0	
		Max	39.0	42.0	
	Height [cm]	N	70	81	
		Mean	158.4	156.9	P=0.1566
		SD	6.4	7.1	
		Min	143.0	143.0	
		Median	159.0	157.0	
		Max	174.0	178.0	
	Weight [kg]	N	71	82	
		Mean	65.8	64.4	P=0.5252
		SD	12.7	12.6	
		Min	41.0	42.5	
		Median	63.0	62.0	
		Max	104.0	105.0	
	Gestation [weeks]	N	73	83	
		Mean	26.6	27.4	P=0.2725
		SD	5.1	3.7	
		Min	12.0	17.0	
		Median	26.0	27.0	
		Max	36.0	36.0	

Table 4.4 below shows the gender, condition of the infant and feeding type. The percentage of male infants is similar in both treatment groups, at about 45%. Few infants were premature. The majority of mothers did not breast feed their infants in both treatment groups. There is no statistically significant difference in these variables between the two treatment groups.

Table 4.4
Demographic Data: Infants
Population: Safety

Visit	Variable	Category	Vitamin A		Placebo		P-value
			n	%	n	%	
				N=75		N=73	
Post-delivery 1 month	Gender	Male	35	46.7	33	45.2	
		Female	40	53.3	40	54.8	0.8585
				N=74		N=70	
	Condition of infant	Term	63	85.1	56	80.0	
		Premature	11	14.9	14	20.0	0.4161
				N=72		N=67	
	Type of feeding	Breast	23	31.9	15	22.4	
		Not breast	43	59.7	45	67.2	
		Both	6	8.3	7	10.4	0.4429

Some information was obtained retrospectively after 1month visit.

The length, head circumference, weight and heart rate for the infants when they were 1 month old are given in Table 4.5. On average the infants were about 54cm long and weighed about 4kg at the age of 1 month in both treatment groups. There is no statistically significant difference in these infant developmental characteristics between the two treatment groups.

Table 4.5
Developmental characteristics: Infants
Population: Safety

Visit	Variable[unit]	Statistic	Vitamin A	Placebo	P-value
Post-delivery 1 month	Length [cm]	N	58	54	
		Mean	53.5	54.6	0.2194
		SD	4.4	4.7	
		Min	42.0	43.0	
		Median	53.0	55.0	
		Max	64.0	69.5	
	Head circumference[cm]	N	58	53	
		Mean	37.7	37.5	0.6123
		SD	2.1	2.7	
		Min	32.0	32.0	
		Median	38.0	38.0	
		Max	43.0	45.0	
	Heart rate[beats/min]	N	55	55	
		Mean	140.3	141.1	0.7134
		SD	11.0	11.3	
		Min	102.0	105.0	
		Median	146.0	146.0	
		Max	156.0	180.0	
	Weight[kg]	N	58	54	
		Mean	4.0	4.2	0.5252
		SD	0.9	1.1	
		Min	2.1	2.0	
		Median	4.0	4.1	
		Max	6.8	6.3	

The means of the height-for-age, weight-for-age and weight-for-height percentiles and z-scores as well as the associated differences, for infants from post-delivery 1 month to post-delivery 18 months visit are given in Table 4.6 below. The mean percentiles did not change markedly from first post-delivery visit to the last visit in both treatment groups. There is no statistically significant difference between the two groups in the mean percentiles and z-scores at all the visits except for weight-for-height z-scores at post-delivery 15 months visit (p=0.0389) with the weight-for-height z-scores higher in the placebo group.

Table 4.6
Percentiles and Z-scores: Infants
Population: Safety

Visit	Variable	Vitamin A	Placebo	Difference	P-value
		Mean	Mean		
Post-delivery 1 months	Height-for-age Percentiles	41.09	48.41	-7.32	0.2814
	Height-for-age Z-score	1.37	1.02	0.36	0.2425
	Weight-for-age Percentiles	38.65	39.59	-0.94	0.8799
	Weight-for-age Z-score	0.81	0.69	0.12	0.4640
	Weight-for-height Percentiles	45.45	40.82	4.63	0.4852
	Weight-for-height Z-score	1.24	0.93	0.31	0.4483
Post-delivery 3 months	Height-for-age Percentiles	39.56	45.67	16.12	0.3250
	Height-for-age Z-score	0.92	1.21	0.29	0.4498
	Weight-for-age Percentiles	46.00	42.28	3.72	0.5309
	Weight-for-age Z-score	0.97	0.86	0.11	0.6058
	Weight-for-height Percentiles	54.04	47.99	6.05	0.3047
	Weight-for-height Z-score	1.18	0.75	0.44	0.0855
Post-delivery 6 months	Height-for-age Percentiles	44.35	46.51	-2.16	0.7434
	Height-for-age Z-score	1.02	1.35	-0.33	0.3552
	Weight-for-age Percentiles	38.50	41.22	-2.72	0.6608
	Weight-for-age Z-score	0.84	0.93	-0.09	0.7009
	Weight-for-height Percentiles	41.67	37.49	4.19	0.4871
	Weight-for-height Z-score	0.83	0.91	-0.08	0.7462
Post-delivery 9 months	Height-for-age Percentiles	45.41	53.00	-7.59	0.2836
	Height-for-age Z-score	1.30	1.69	-0.39	0.3813
	Weight-for-age Percentiles	28.72	38.77	-10.05	0.1082
	Weight-for-age Z-score	0.70	0.81	-0.11	0.5882
	Weight-for-height Percentiles	28.69	32.14	-3.45	0.5319
	Weight-for-height Z-score	0.47	0.65	-0.18	0.3763
Post-delivery 12 months	Height-for-age Percentiles	46.65	54.12	-7.47	0.2943
	Height-for-age Z-score	1.21	1.18	0.03	0.8793
	Weight-for-age Percentiles	26.04	35.44	-9.40	0.1368
	Weight-for-age Z-score	0.83	0.80	0.03	0.9119
	Weight-for-height Percentiles	23.98	30.13	-6.15	0.3055
	Weight-for-height Z-score	1.08	0.88	0.20	0.5861
Post-delivery 15 months	Height-for-age Percentiles	54.21	55.34	-1.13	0.8765
	Height-for-age Z-score	1.25	1.35	-0.11	0.8067
	Weight-for-age Percentiles	29.56	38.63	-9.07	0.1814
	Weight-for-age Z-score	0.76	0.74	0.02	0.9408
	Weight-for-height Percentiles	25.34	32.85	-7.51	0.2257
	Weight-for-height Z-score	0.46	0.88	-0.42	0.0389
Post-delivery 18 months	Height-for-age Percentiles	51.63	50.18	1.45	0.8469
	Height-for-age Z-score	1.15	1.25	-0.11	0.6844
	Weight-for-age Percentiles	27.01	33.51	-6.50	0.2970
	Weight-for-age Z-score	0.71	0.74	-0.03	0.9087
	Weight-for-height Percentiles	23.88	26.61	-2.73	0.6142
	Weight-for-height Z-score	0.80	0.59	0.21	0.5126

The percentages of infants with percentiles lower than the 3rd percentile from post-delivery 1 month to post-delivery 18 months visit are given in Table 4.7 below. Less than 40% of infants have percentiles lower than the 3rd percentile in both treatment groups at

any visit. The percentages of infants with percentiles lower than the 3rd percentile are higher in vitamin A group than those in the placebo group as from post-delivery 12 months to post-delivery 18 months visit. There is no statistically significant difference in the percentages of infants with percentiles lower than the 3rd percentile at all the visits except for weight-for-height at post-delivery 12 and 15 months between the two groups.

Table 4.7
Percentages of infants with percentiles lower than the 3rd Percentile
Population: Safety

Visit	Variable	Vitamin A		Placebo		P-value
		n	%	n	%	
			N=51		N=47	
Post-delivery 1 month	<3rd Height-for-age percentile	9	17.7	3	6.4	0.0892
			N=58		N=54	
	< 3rd Weight-for-age percentile	9	15.5	11	20.4	0.5028
	<3rd Weight-for-height percentile	3	5.9	4	8.5	0.6138
			N=61		N=58	
Post-delivery 3 months	<3rd Height-for-age percentile	6	9.8	7	12.1	0.6963
			N=63		N=60	
	< 3rd Weight-for-age percentile	6	9.5	8	13.3	0.5061
			N=61		N=57	
	<3rd Weight-for-height percentile	5	8.2	4	7.0	0.8094
			N=56		N=56	
Post-delivery 6 months	<3rd Height-for-age percentile	12	21.4	9	16.1	0.4677
			N=57		N=57	
	< 3rd Weight-for-age percentile	10	17.5	12	21.1	0.6350
	<3rd Weight-for-height percentile	8	14.3	8	14.3	1.0000
			N=55		N=53	
Post-delivery 9 months	<3rd Height-for-age percentile	8	14.6	4	7.6	0.2473
					N=52	
	< 3rd Weight-for-age percentile	12	21.8	9	17.3	0.5571
					N=52	
	<3rd Weight-for-height percentile	9	16.4	10	19.2	0.6981
			N=50		N=51	
Post-delivery 12 months	<3rd Height-for-age percentile	5	10.0	5	9.8	0.9737
	< 3rd Weight-for-age percentile	17	34.0	11	21.6	0.1629
	<3rd Weight-for-height percentile	19	38.0	8	15.7	0.0113
			N=44		N=45	
Post-delivery 15 months	<3rd Height-for-age percentile				N=46	
		5	11.4	1	2.2	0.0806
	< 3rd Weight-for-age percentile	8	18.2	8	17.8	0.9604
	<3rd Weight-for-height percentile	16	36.4	7	15.6	0.0250
			N=42		N=43	
Post-delivery 18 months	<3rd Height-for-age percentile	5	11.9	2	4.7	0.2239
	< 3rd Weight-for-age percentile	9	21.4	9	20.9	0.9552
	<3rd Weight-for-height percentile	14	33.3	7	16.3	0.0684

4.2.2 HIV Symptoms as assessed by medical history

Mothers

Table 4.8 shows the percentages of patients with HIV symptoms at recruitment. The most common symptom was headache followed by coughing and fever in both groups. The same pattern is observed in the ITT population. There is no statistically significant difference in all HIV symptoms recorded except for night sweats (p=0.0117) between the two treatment groups for the ITT population with night sweats being more common in the vitamin A group.

Table 4.8
HIV symptoms on medical history at Recruitment: Mothers
Population: Safety/ITT

Population	Variable	Vitamin A		Placebo		
		n	%	n	%	
			N=152		**N=150**	
Safety	Night sweats	24	15.8	10	6.7	
	Coughing	33	21.7	30	20.0	
			N=150	21	14.0	
	Fever	28	18.7			
			N=151		**N=149**	
	Nausea/Vomiting	12	7.9	10	6.7	
					N=148	
	Headache	52	34.2	50	33.8	
			N=130		**N=133**	
	Confusion	3	2.3	4	3.0	
			N=73		**N=84**	
ITT	Night sweats	11	15.1	3	3.6	P=0.0117
	Coughing	19	26.0	18	21.4	P=0.4983
			N=71			
	Fever	13	18.3	13	15.5	P=0.6380
			N=72		**N=83**	
	Nausea/Vomiting	6	8.3	6	7.2	P=0.7975
					N=83	
	Headache	24	32.9	30	36.1	P=0.6686
			N=65		**N=76**	
	Confusion	2	3.1	2	2.6	P=0.8738

Infants

The percentages of HIV symptoms recorded in infants at the age of 1 month are shown in Table 4.9 More infants in the placebo group were coughing when they were seen for the first time compared to those in the vitamin A group. There is no statistically significant difference in these symptoms between the two treatment groups.

Table 4.9
HIV symptoms on medical history: Infants
Population: Safety

Visit		Vitamin A N=58		Placebo N=55		P-value
		n	%	n	%	
Post-delivery1 months	Night sweats	0	0.0	0	0.0	
	Coughing	2	3.4	4	7.3	0.3648
	Fever	2	3.4	1	1.8	0.5901
	Nausea/Vomiting	2	3.4	1	1.8	0.5901

4.2.3 HIV related abnormalities when assessed by physical examination

Mothers

The HIV related abnormalities found during physical examination at recruitment are shown in Table 4.10. The most common abnormalities were lymphadenopathy in both treatment groups, followed by abnormalities of ears, nose and throat in vitamin A and anemia and jaundice in the placebo group. About 12% and 13% of the patients had lymphadenopathy at recruitment in vitamin A and placebo groups respectively in the safety population.

Nearly 7% and 9% of patients had skin abnormalities in placebo and vitamin A groups respectively, but no karposi sarcoma was diagnosed in any patient. The distribution of the abnormalities is similar in both groups for patients in the ITT population. The percentages of patients with abnormalities are not statistically significantly different

between the two groups for the ITT population except for abnormalities in the respiratory systems (which occurred more frequently in vitamin A group (5.5%) versus (0%) in the placebo group) with a p-value of 0.0298. However, the observed difference is not clinically significant because of the small numbers involved.

Table 4.10
Abnormalities on physical examination at Recruitment: Mothers
Population: Safety/ITT

Population	Variable	Vitamin A		Placebo		
		n	%	n	%	
			N=152		N=150	
Safety	Anaemia /Jaundice	12	7.9	11	7.3	
	Lymphadenopathy	18	11.8	20	13.3	
	Cardio-Vascular System (CVS)	4	2.6	4	2.7	
	Gastro-Intestinal Tract (GIT)	3	2.0	0	0.0	
			N=147		N=146	
	Unitary Gut (UG)	12	8.2	11	7.5	
	Central Nervous System (CNS)	1	0.7	0	0.0	
					N=148	
	Ears, Nose, and Throat (ENT)	16	10.5	8	5.4	
	Skin	14	9.2	10	6.7	
	Respiratory System	8	5.3	0	0.0	
			N=73		N=84	
ITT	Anaemia /Jaundice	8	11.0	7	8.3	P=0.5767
	Lymphnodes	10	13.7	14	16.7	P=0.6062
	Cardio-Vascular System (CVS)	2	2.7	2	2.4	P=0.8868
	Gastro-Intestinal Tract (GIT)	2	2.7	0	0.0	P=0.2039
			N=70		N=80	
	Unitary Gut (UG)	7	10.0	6	7.5	P=0.6994
	Central Nervous System (CNS)	1	1.4	0	0.0	P=0.2819
					N=82	
	Ears, Nose, and Throat (ENT)	8	11.0	4	4.9	P=0.1574
	Skin	4	5.5	8	9.5	P=0.3414
	Respiratory System	4	5.5	0	0.0	P=0.0298

Infants

The HIV related abnormalities found in infants at the age of 1 month are given in Table 4.11 below. Of those infants with abnormalities, most babies (nearly 7% and 6% in vitamin A and placebo groups respectively) had skin abnormalities when they were seen for the first time. There is no statistically significant difference in the abnormalities found in infants between the two treatment groups.

Table 4.11
Abnormalities on physical examination: Infants
Population: Safety

	Variable	Vitamin A		Placebo		P-value
		n	%	n	%	
			N=58		N=53	
Post-delivery 1 month			N=57			
	General appearance	1	1.8	0	0.0	0.3238
					N=55	
	Skin	4	6.9	3	5.5	0.7506
	Eyes	0	0.0	0	0.0	
	Musculoskeletal	0	0.0	0	0.0	
			N=57			
	ENT	3	5.3	1	1.9	0.3445

4.2.4 Vital Signs: Mothers

The vital signs per treatment group are given in Table 4.12. The mean SBP for vitamin A and placebo groups is about 113 and 111mmHg, respectively in the safety population. The percentages of patients with hypertension are similar in both treatment groups. The mean heart rate was about 75 in the safety population and 76 in the ITT population for both groups. There is no statistically significant difference in vital signs between the two groups for the ITT population.

Table 4.12
Vital signs at Recruitment: Mothers
Population: Safety/ITT

Population	Variable[unit]	Statistic	Vitamin A	Placebo	
Safety	Systolic blood pressure[mmHg]	N	152	150	
		Mean	112.7	110.8	
		SD	12.4	10.6	
		Min	80.0	90.0	
		Median	110.0	110.0	
		Max	150.0	150.0	
	Diastolic blood pressure[mmHg]	N	152	150	
		Mean	65.5	63.1	
		SD	11.9	11.2	
		Min	40.0	40.0	
		Median	70.0	60.0	
		Max	96.0	90.0	
	Hypertension	n/N	7/152	3/150	
		%	4.6	2.0	
	Heart rate[beats/min]	N	141	135	
		Mean	75.5	75.2	
		SD	9.3	8.7	
		Min	58.0	58.0	
		Median	75.0	74.0	
		Max	120.0	102.0	
ITT	Systolic blood pressure[mmHg]	N	73	84	
		Mean	112.2	109.1	P=0.0828
		SD	11.4	11.0	
		Min	90.0	90.0	
		Median	110.0	110.0	
		Max	145.0	150.0	
	Diastolic blood pressure[mmHg]	N	73	84	
		Mean	64.0	63.2	P=0.6833
		SD	11.2	11.2	
		Min	40.0	40.0	
		Median	60.0	60.0	
		Max	90.0	90.0	
	Hypertension	n/N	1/73	1/84	
		%	1.4	1.2	P=0.9204
	Heart rate[beats/min]	N	69	76	
		Mean	76.4	76.3	P=0.9362
		SD	10.6	8.8	
		Min	58.0	58.0	
		Median	74.0	76.0	
		Max	120.0	100.0	

4.2.5 Obstetrical data: Mothers

Table 4.13 gives the obstetrical status of patients at recruitment. The majority (more than 90%) of patients were recruited when they were in their 3rd trimester. Only 3 patients were recruited when they were in the 1st trimester. Most patients had a gravity of 2 or more, parity of 0 in vitamin A group and 1 in placebo group. There is no statistically significant difference in these obstetrical variables between the two treatment groups for the ITT population.

Table 4.13
Obstetrical status at Recruitment: Mothers
Population: Safety/ITT

Population	Characteristic		Vitamin A		Placebo		
			n	%	n	%	
				N=152		N=151	
Safety	Gestational age	1st trimester	1	0.7	2	1.3	
		2nd trimester	12	7.9	9	6.0	
		3rd trimester	139	91.5	140	92.7	
				N=151		N=147	
	Parity	P(0)	62	41.1	48	32.7	
		P(1)	60	39.7	61	41.5	
		P(2 or more)	29	19.2	38	25.9	
	Gravity	G(1)	61	40.4	47	32.0	
		G(2 or more)	90	59.6	100	68.0	
				N=73		N=83	
ITT	Gestational age	1st trimester	1	1.4	2	2.4	
		2nd trimester	7	9.6	2	2.4	P=0.1370
		3rd trimester	65	89.0	81	95.3	
	Parity	P(0)	32	43.8	29	34.9	
		P(1)	29	39.7	36	43.4	P=0.4804
		P(2 or more)	12	16.4	18	21.7	
	Gravity	G(1)	32	43.8	28	33.7	
		G(2 or more)	41	56.2	55	66.3	P=0.1957

Modes of delivery are given in Table 4.14. Most mothers had a vaginal delivery in both groups. There was no instrumental delivery. There is no statistically significant difference in mode of delivery between the two groups. Of those mothers who had vaginal delivery 52.2% and 50% in vitamin A and placebo groups respectively had episiotomy.

Table 4.14
Mode of Delivery: Mothers
Population: Safety

Variable	Characteristic	Vitamin A		Placebo		P-value
		n	%	n	%	
			N=73		N=73	
Mode of delivery	Vaginal	47	64.4	54	74.0	
	Caesar	26	35.6	19	26.0	
	Instrumental	0	0.0	0	0.0	0.2096
			N=46		N=54	
Episiotomy	Yes	24	52.2	27	50.0	
	No	22	47.8	27	50.0	0.8284

1 patient had episiotomy missing in vitamin A group

Delivery procedures, duration of labour and duration of ruptured membranes in relation to time of delivery were unfortunately not collected.

4.2.6 Laboratory data

Mothers

Full blood counts per treatment group are given in Table 4.15. The means of all blood counts are similar for the two treatment groups. There is no statistically significant difference in the full blood counts between the two groups for the ITT population.

Table 4.15
Full blood counts at Recruitment: Mothers
Population: Safety /ITT

Population	Variable[unit]	Statistic	Vitamin A	Placebo
Safety	Haemoglobin [g/dl]	N	151	146
		Mean	11.04	11.01
		SD	1.26	1.33
		Min	8.10	5.80
		Median	11.00	11.10
		Max	14.10	16.20
	Haematocrit [L/L]	N	151	146
		Mean	0.336	0.335
		SD	0.035	0.037
		Min	0.260	0.210
		Median	0.340	0.340
		Max	0.420	0.480
	Red blood cells [10^9 cells/litre]	N	150	146
		Mean	3.759	3.775
		SD	0.403	0.370
		Min	2.700	2.850
		Median	3.700	3.790
		Max	5.270	5.200
	White blood cells [10^9 cells/litre]	N	150	146
		Mean	6.78	6.76
		SD	2.02	1.84
		Min	3.10	2.70
		Median	6.50	6.50
		Max	13.60	11.70
	Lymphocytes [10^9 cells/litre]	N	151	146
		Mean	1.77	1.74
		SD	0.61	0.58
		Min	0.40	0.70
		Median	1.70	1.70
		Max	4.20	4.60
	Neutrophils [10^9 cells/litre]	N	151	146
		Mean	4.41	4.49
		SD	1.59	1.54
		Min	1.60	1.10
		Median	4.20	4.30
		Max	9.30	9.80
	Monocytes [10^9 cells/litre]	N	151	146
		Mean	0.377	0.362
		SD	0.147	0.149
		Min	0.100	0.090
		Median	0.360	0.310
		Max	1.090	0.96
	Eosinophils [10^9 cells/litre]	N	150	145
		Mean	0.138	0.131
		SD	0.134	0.128
		Min	0.000	0.000
		Median	0.100	0.100
		Max	1.010	0.630
	Thrombocytes [10^9 cells/litre]	N	151	146
		Mean	265.0	272.4
		SD	76.9	68.3
		Min	100.0	130.0
		Median	250.0	269.0
		Max	543.0	476.0

Population	Variable[unit]	Statistic	Vitamin A	Placebo	
ITT	Haemoglobin [g/dl]	N	72	83	
		Mean	11.17	11.00	P=0.4284
		SD	1.31	1.30	
		Min	8.10	5.80	
		Median	11.25	11.10	
		Max	14.10	16.20	
	Haematocrit [L/L]	N	72	83	
		Mean	0.340	0.337	P=0.5708
		SD	0.037	0.036	
		Min	0.260	0.210	
		Median	0.340	0.340	
		Max	0.420	0.480	
	Red blood cells [10^9 cells/litre]	N	71	83	
		Mean	3.768	3.775	P=0.9155
		SD	0.433	0.375	
		Min	3.070	2.850	
		Median	3.700	3.790	
		Max	4.710	5.200	
	White blood cells [10^9 cells/litre]	N	71	83	
		Mean	6.70	6.94	P=0.4189
		SD	1.91	1.74	
		Min	3.20	3.20	
		Median	6.70	6.80	
		Max	13.60	11.70	
	Lymphocytes [10^9 cells/litre]	N	72	83	
		Mean	1.72	1.82	P=0.2882
		SD	0.53	0.64	
		Min	0.40+	0.70+	
		Median	1.75	1.80	
		Max	3.80*	4.60*	
	Neutrophils [10^9 cells/litre]	N	72	83	
		Mean	4.32	4.58	P=0.2778
		SD	1.51	1.46	
		Min	1.60	2.00	
		Median	4.18	4.50	
		Max	8.02	9.00	
	Monocytes [10^9 cells/litre]	N	72	83	
		Mean	0.386	0.367	P=0.4323
		SD	0.153	0.146	
		Min	0.100	0.090	
		Median	0.380	0.320	
		Max	1.091	0.840	
	Eosinophils [10^9 cells/litre]	N	71	83	
		Mean	0.15	0.13	P=0.3481
		SD	0.16	0.13	
		Min	0.00	0.00	
		Median	0.10	0.10	
		Max	1.01	0.63	
	Thrombocytes [10^9 cells/litre]	N	72	83	
		Mean	267.76	267.80	P=0.9949
		SD	69.48	62.80	
		Min	125.00	134.00	
		Median	256.00	262.00	
		Max	496.00	476.00	

* Values are abnormally high. + Values are abnormally low. Study doctors believe that the patients may have had other unknown infections at that time when blood was drawn.

The T-cell counts are given in Table 4.16. On average the T-cell counts are similar for the two treatment groups. There is no statistically significant difference in T-cell counts between the two treatment groups for the ITT population.

Table 4.16
T-cell counts at Recruitment: Mothers
Population: Safety/ITT

Population	Variable[unit]	Statistic	Vitamin A	Placebo	
Safety	CD4 counts [10^9 cells/litre]	N	150	148	
		Mean	0.434	0.446	
		SD	0.209	0.196	
		Min	0.020	0.050	
		Median	0.420	0.430	
		Max	1.260	1.090	
	CD8 counts [10^9 cells/litre]	N	150	148	
		Mean	0.88	0.85	
		SD	0.39	0.37	
		Min	0.14	0.20	
		Median	0.85	0.82	
		Max	2.58*	2.43*	
	CD4/CD8 ratio	N	150	148	
		Mean	0.555	0.598	
		SD	0.345	0.319	
		Min	0.030	0.050	
		Median	0.470	0.515	
		Max	1.830	2.000	
ITT	CD4 counts[10^9 cells/litre]	N	71	83	
		Mean	0.44	0.46	P=0.4484
		SD	0.19	0.20	
		Min	0.09	0.05	
		Median	0.43	0.45	
		Max	0.96	1.09	
	CD8 counts[10^9 cells/litre]	N	71	83	
		Mean	0.89	0.88	P=0.8311
		SD	0.37	0.40	
		Min	0.14	0.25	
		Median	0.84	0.82	
		Max	2.25	2.43	
	CD4/CD8 ratio	N	71	83	
		Mean	0.54	0.58	P=0.3881
		SD	0.29	0.32	
		Min	0.09	0.05	
		Median	0.46	0.51	
		Max	1.44	2.00	

* Values are abnormally high. Study doctors believe that the patient may have had an unknown infection at the time when the blood was drawn.

Infants

Table 4.17 shows the full blood counts for the infants at the age of 3 months. There is no statistically significant difference in full blood counts between the two groups for the infants. The difference between the two groups with regards to eosinophils is close to statistical significance (p=0.0570).

Table 4.17
Full blood counts: Infants
Population: Safety

Visit	Variable[unit]	Statistic	Vitamin A	Placebo	P-value
Post-delivery 3 months	Haemoglobin[g/dl]	N	59	63	
		Mean	10.20	10.12	0.6413
		SD	0.91	1.00	
		Min	7.60	7.20	
		Median	10.30	10.20	
		Max	13.70	12.10	
	Haematocrit[L/L]	N	59	63	
		Mean	0.310	0.307	0.6186
		SD	0.029	0.031	
		Min	0.250	0.230	
		Median	0.310	0.310	
		Max	0.430	0.400	
	Red blood cells[10^9 cells/litre]	N	59	63	
		Mean	3.865	3.832	0.6735
		SD	0.385	0.463	
		Min	3.120	2.890	
		Median	3.860	3.820	
		Max	4.900	5.280	
	White blood cells[10^9 cells/litre]	N	59	63	
		Mean	11.24	10.26	0.1814
		SD	4.55	3.42	
		Min	5.60	4.00	
		Median	10.60	10.10	
		Max	32.60	19.60	
	Lymphocytes[10^9 cells/litre]	N	59	63	
		Mean	6.91	6.42	0.2841
		SD	2.75	2.19	
		Min	1.80	0.21+	
		Median	6.50	6.20	
		Max	18.70*	11.40*	
	Neutrophils[10^9 cells/litre]	N	59	63	
		Mean	2.87	2.62	0.3669
		SD	1.65	1.45	
		Min	0.60+	0.60+	
		Median	2.50	2.10	
		Max	8.70	8.00	
	Monocytes[10^9 cells/litre]	N	59	63	
		Mean	0.896	0.772	0.1464
		SD	0.552	0.366	
		Min	0.350	0.210	
		Median	0.780	0.660	
		Max	3.880*	2.230*	
	Eosinophils[10^9 cells/litre]	N	59	63	
		Mean	0.419	0.305	0.0570
		SD	0.400	0.242	
		Min	0.010	0.000	
		Median	0.270	0.210	
		Max	1.940	1.220	
	Thrombocytes[10^9 cells/litre]	N	59	63	
		Mean	399.7	380.3	0.4354
		SD	140.9	134.0	
		Min	29.0	54.0	
		Median	417.0	401.0	
		Max	841.0	617.0	

*Values are abnormally high. +Values are abnormally low. Study doctors believe that the patients may have had other unknown infection at the time when the blood was drawn.

The T-cell counts for the infants at the age of 3 months are given in Table 4.18. The counts are similar in both groups. There is no statistically significant difference in the T-cell counts between the two treatment groups for the infants.

Table 4.18
T-cell counts: Infants
Population: Safety

Visit	Variable[unit]	Statistic	Vitamin A	Placebo	P-value
Post-delivery 3 months	CD4 counts[10^9 cells/litre]	N	54	57	
		Mean	2.419	2.267	0.4383
		SD	1.070	0.989	
		Min	0.720	0.300	
		Median	2.270	2.080	
		Max	6.530	4.770	
	CD8 counts[10^9 cells/litre]	N	54	57	
		Mean	1.67	1.44	0.2770
		SD	1.19	1.01	
		Min	0.36	0.26	
		Median	1.48	1.12	
		Max	6.62	5.43	
	CD4/CD8 ratio	N	54	57	
		Mean	2.480	2.049	0.9974
		SD	1.257	1.373	
		Min	0.210	0.340	
		Median	2.030	1.830	
		Max	5.240	7.890	

4.3 Comparison of data at each post-natal visit for the safety population

4.3.1 HIV symptoms as assessed by medical history: Mothers and Infants

Very few patients (mothers or infants) had HIV symptoms at any of the visits in both treatment groups. There is no clinically significant change in the percentages of HIV symptoms recorded at post-delivery 1 month through to 18 months visit for mothers (see Appendix 16). At each visit there is no statistically significant difference in the HIV symptoms between the two groups. A similar pattern is observed for the infants (see Appendix 17). There is no statistically significant difference in any symptom at any visit

between the two groups except coughing (p-value=0.0044) at visit post-delivery 15 months for the infants with coughing being more common in the placebo group.

4.3.2 HIV related abnormalities when assessed by physical examination: Mothers and Infants

Very few patients (both mothers and infants) had HIV related abnormalities at any of the visits in both treatment groups. The percentages of the abnormalities observed at each visit for the mothers are given in Appendix 18. These percentages did not change significantly from one visit to another. There is no statistically significant difference in any abnormality observed at any visit between the two groups except skin at post-delivery 12 months (p=0.0223) visit with skin abnormalities being more common in vitamin A group than in the placebo group. The percentages of abnormalities for the infants for all the visits are shown in Appendix 19. For all the visits there is no statistically significant difference in the percentages of abnormalities observed in infants between the two treatment groups except for skin at post-delivery 15 months (p=0.0045) which occurred more frequently in vitamin A group.

4.3.3 Vital signs: Mothers

The vital signs recorded at each post-natal visit are similar in both treatment groups (see Appendix 20). Mother's weight at post-delivery 1 month was not measured. The mean weight of the mothers was about 60 kg at all the visits. There is no statistically significant difference in mothers' vital signs and weight at any visit between the treatment groups.

4.3.4 Laboratory data: Mothers and Infants

Full blood and T-cell counts observed in mothers over the visits are similar (see Appendix 21). There are no statistically significant differences in full blood counts and T-cell counts at any visit between the two treatment groups, except for monocytes and eosinophils at post-delivery 3 months visit with vitamin A having relatively higher means of monocytes and eosinophils than the placebo group. The full blood counts and T-cell counts for infants are similar over the visits (see Appendix 22). There is no statistically significant difference in full blood counts and T-cell counts observed in infants at any visit between the two treatment groups.

4.3.5 Infant developmental characteristics

The developmental characteristics (length, weight, head circumference and heart rate) for the infants are given in Appendix 23. All the developmental characteristics are similar between the two groups at all the visits. There is no statistically significant difference in any developmental characteristic at any visit between the two groups.

4.4 Efficacy results

4.4.1 Primary efficacy outcome: Effect of vitamin A on HIV transmission rate

Table 4.19 below shows the vertical HIV transmission rate per analysis population. For the ITT population the transmission rate in vitamin A group is 19.2% whereas in the placebo group it is 21.2%. There is no significant difference between these two rates

(95% CI -14.5% to 10.5%; p-value=0.76). The % efficacy of vitamin A for the ITT population is {[(21.2-19.2)/21.2] x 100}= 9.4%, which is very low.

Table 4.19
HIV transmission rates
Population: ITT/PP

	Vitamin A		Placebo	
ITT population	n/N	%	n/N	%
	14/73	19.2	18/85	21.2
Point estimate (Vitamin A-Placebo)	-2.0%			
95% CI	-14.5% ; 10.5%			
P-value	0.7553			
PP population				
	10/50	20.0	12/54	22.2
Point estimate (Vitamin A-Placebo)	-2.2%			
95% CI	-17.9% ; 13.5%			
P-value	0.7816			

For the PP population the vertical transmission rate in vitamin A group is 20.0% whereas in the placebo group it is 22.2% (see Table 4.19 above). Again, there is no significant difference between these two rates, with a 95% CI of -17.9% to 13.5%. The % efficacy of vitamin A for the PP population is {[(22.2-20.0)/22.2] x 100}=9.9%. This efficacy is only slightly higher than that which was obtained in the ITT population. These results suggest that vitamin A is not effective in reducing mother to child transmission rates.

Four infants in the ITT population (2.5%) were late converters. Infant number 84 and 222 became HIV positive after 3 months whereas infant number 45 and 178 became HIV positive from 12 months.

Table 4.20 shows the results of the logistic regression model fitted to assess the effect of maternal vitamin A supplementation on vertical transmission. Vitamin A is not

significantly associated with HIV status of the infant (p-value=0.6548) after controlling for baseline CD4 and CD8, log transformed (see Table 4.20 below). The odds of an infant to be HIV positive for patients receiving vitamin A is approximately 0.83 times that of the infants in the placebo group. The 95% CI (0.365; 1.883) for this odds ratio includes 1, which indicates that vitamin A did not have a statistically significantly protective effect.

Table 4.20
Logistic regression results

Parameter	Estimates	Standard error	Chi-squared	P-value	Odds ratio	95%CI
Intercept	-2.1018	0.4674	20.2176	0.0001		
Treatment	-0.1870	0.4183	0.1999	0.6548	0.829	0.365; 1.883
Log CD4	-0.7192	0.3891	3.4156	0.0646	0.487	0.227; 1.044
Log CD8	-0.2809	0.4714	0.3551	0.5512	0.755	0.300; 1.902

4.4.2 Secondary efficacy outcomes: Effect of vitamin A on HIV symptoms by history

Mothers

The potential effect of treatment on HIV symptoms was investigated. HIV symptoms recorded in mothers at post-delivery 3 and 18 months are summarised in Table 4.21 for the ITT population and at post-delivery 3 months for the PP population. Very few patients had HIV symptoms in either analysis population. These symptoms are not statistically significantly associated with treatment at any post-delivery visit for either the ITT population (see Appendix 24) or PP population at 3 months.

Table 4.21
HIV symptoms on medical history: Mother
Population: ITT/PP

Population	Visit	Variable	Vitamin A		Placebo		P-value
			n	%	n	%	
				N=63		N=74	
ITT	Post-natal 3 months	Night sweats	2	3.2	1	1.4	0.4674
		Coughing	1	1.6	3	4.1	0.3927
		Fever	2	3.2	0	0.0	0.1226
		Nausea/Vomiting	0	0.0	0	0.0	
		Headache	2	3.2	4	5.4	0.5248
		Confusion	0	0.0	0	0.0	
				N=41		N=49	
	Post natal 18 months	Night sweats	0	0.0	0	0.0	
		Coughing	1	2.4	5	10.2	0.1414
		Fever	0	0.0	0	0.0	
		Nausea/Vomiting	0	0.0	0	0.0	
		Headache	3	7.3	3	6.1	0.8210
		Confusion	0	0.0	0	0.0	
				N= 49		N=53	
PP	Post-natal 3 months	Night sweats	2	4.1	1	1.9	0.5122
		Coughing	1	1.0	0	0.0	0.2960
		Fever	2	4.1	0	0.0	0.1374
		Nausea/Vomiting	0	0.0	0	0.0	
		Headache	1	2.0	1	1.9	0.9553
		Confusion	0	0.0	0	0.0	

Infants

Table 4.22 shows the percentages of HIV symptoms recorded in infants at post-delivery 3 and 18 months for the ITT population and at 3 months for the PP population. The difference in percentages of infants with night sweats is close to statistical significance (p=0.0597) with night sweats more common in vitamin A group for the ITT population at 3 months. Few infants had HIV symptoms for either analysis population. The most prevalent symptom was coughing. None of these symptoms was statistically significantly

associated with the treatment at any visit (see Appendix 25) except for coughing at post-delivery 3 months (p=0.0036) with coughing being more common in the vitamin A group.

Table 4.22
HIV symptoms on medical history: Infant
Population: ITT/PP

Population	Visit	Variable	Vitamin A		Placebo		P-value
			N	%	n	%	
				N=64		N=74	
ITT	Post-natal 3 months	Night sweats	3	4.7	0	0.0	0.0597
		Coughing	7	10.9	6	8.1	0.5704
		Fever	3	4.7	2	2.7	0.5338
		Nausea/Vomiting	2	3.1	1	1.4	0.4837
				N=41		N =49	
	Post-natal 18 months	Night sweats	1	2.4	0	0.0	0.2716
		Coughing	4	9.8	7	14.3	0.5234
		Fever	0	0.0	0	0.0	
		Nausea/Vomiting	0	0.0	0	0.0	
				N= 50		N=53	
PP	Post-natal 3 months	Night sweats	2	4.0	0	0.0	0.1415
		Coughing	4	8.0	3	5.7	0.6373
		Fever	0	0.0	0	0.0	
						N=52	
		Nausea/Vomiting	0	0.0	1	1.9	0.3244

4.4.3 Secondary efficacy outcomes: Effect of vitamin A on HIV related abnormalities observed during physical examination

Mothers

Percentages of HIV related abnormalities observed in mothers at post-delivery 3 and 18month visits are given in Table 4.23 for the ITT population and at 3 months for the PP population. Only very few patients showed any abnormalities. None of the abnormalities were statistically significantly associated with treatment at any post-natal visit (see Appendix 26) except for skin abnormalities at post-delivery 12 months (p=0.0223) with skin abnormalities more frequent in vitamin A group.

Table 4.23
Abnormalities on physical examination: Mother
Population: ITT/PP

Population	Visit	Variable	Vitamin A		Placebo		P-value
			N	%	N	%	
				N=64		N=74	
ITT	Post-natal 3 months	Anaemia/Jaundice	0	0.0	0	0.0	
		Lymphadenopathy	0	0.0	1	1.4	0.3506
		CVS	0	0.0	0	0.0	
		GIT	0	0.0	0	0.0	
		UG	2	3.1	0	0.0	0.1888
		CNS	0	0.0	0	0.0	
		ENT	2	3.1	2	2.7	0.8828
		Skin	3	4.7	1	1.4	0.2440
		Respiratory	0	0.0	0	0.0	
				N=41		N=49	
	Post-natal 18 months	Anaemia /Jaundice	0	0.0	3	6.1	0.1071
		Lymphadenopathy	1	2.4	0	0.0	0.2765
		CVS	0	0.0	1	2.1	0.3527
		GIT	0	0.0	0	0.0	
		UG	0	0.0	0	0.0	
		CNS	0	0.0	0	0.0	
		ENT	0	0.0	0	0.0	
		Skin	0	0.0	4	8.2	0.0993
		Respiratory	0	0.0	0	0.0	
PP				N= 50		N=53	
	Post-natal 3 months	Anaemia /Jaundice	0	0.0	0	0.0	
		Lymphadenopathy	0	0.0	1	1.9	0.3290
		CVS	0	0.0	0	0.0	
		GIT	0	0.0	0	0.0	
		UG	2	4.0	0	0.0	0.0660
		CNS	0	0.0	0	0.0	
		ENT	2	4.0	2	3.8	0.9526
		Skin	3	6.0	1	1.9	0.2802
		Respiratory	0	0.0	0	0.0	

Infants

Table 4.24 shows the percentages of abnormalities observed in infants at post-delivery 3 and 18 months visits for the ITT population and at 3 months for the PP population. Few patients had abnormalities in either analysis population. The most frequent abnormalities concerned skin and general appearance of the infants. These abnormalities are not statistically significantly associated with the treatment at any visit (see Appendix 27)

except for skin abnormalities (p=0.0068) at post-delivery 15 months visit with abnormalities more frequent in the vitamin A group.

Table 4.24
Abnormalities on physical examination: Infant
Population: ITT /PP

Population	Visit	Variable	Vitamin A		Placebo		P-value
			n	%	n	%	
			N=62		N=74		
ITT	Post-natal 3 months	General appearance	5	8.1	5	6.7	0.7542
		Skin	5	8.1	7	9.5	0.7751
		Eyes	1	1.6	1	1.4	0.8996
					N=73		
		Musculoskeletal	0	0.0	0	0.0	
		ENT	4	6.5	6	8.1	0.5170
			N=41		N=49		
	Post-natal 18 months	General appearance	4	9.8	2	4.1	0.2825
		Skin	6	14.7	4	8.2	0.3306
		Eyes	0	0.0	1	2.0	0.3576
		Musculoskeletal	1	2.4	0	0.0	0.2716
		ENT	1	2.4	4	8.2	0.2377
			N=48		N=54		
PP	Post-natal 3 months	General appearance	1	2.1	4	7.4	0.2138
		Skin	2	4.2	4	7.4	0.4875
		Eyes	0	0.0	0	0.0	
		Musculoskeletal	0	0.0	0	0.0	
		ENT	3	6.3	4	7.4	0.8175

4.4.4 Vital signs: Mothers

Appendix 28 shows the vital signs for the mothers for all post-delivery visits for the ITT population. These vital signs are not statistically significantly associated with treatment at any of the post-delivery visits. Both mothers and infants in the ITT population had normal heart sounds.

4.5 Summary: Efficacy

Nearly 48% of the 303 study participants were excluded from the ITT efficacy analysis. Of those 145 excluded about 88% did not attend any post-delivery visit. The majority of the 303 study participants were black and Sotho speaking women in both treatment groups. On average patients were recruited when they were 27 weeks pregnant and were 26 years old, in both treatment groups. Demographic, vitals signs and HIV related variables as well as full blood and T-cell counts were similar between the treatment groups for the safety, ITT and PP population at recruitment. None of the variables used to assess HIV symptoms was statistically significantly different between the two treatment groups for the ITT population. Very few (less than 5%) patients had hypertension in either treatment group at recruitment. More than 90% of patients were recruited when they were in the 3rd trimester in both treatment groups and both analysis populations. Nearly 36% and 26% of mothers had caesarean sections in vitamin A and placebo groups respectively.

The developmental characteristics, demographic and HIV symptoms variables as well as full blood and T-cell counts for the infants are similar between the two treatment groups. About 60% and 67% of the infants in vitamin A and placebo groups respectively were not breast-fed. Nearly 7% and 6% of infants in vitamin A and placebo groups respectively had skin abnormalities when they were seen for the first time. Less than 40% of infants had height-for-age, weight-for-age and weight-for-height percentiles less than the 3rd percentile in both groups at all the visits.

The HIV transmission rates were 19.2% and 21.2% for vitamin A and placebo groups respectively (ITT population). There is no statistically significant difference in the transmission rates between vitamin A and placebo groups (p=0.76). Vitamin A efficacy for both ITT and PP analysis populations was less than 10%.

There was no statistically significant difference in the percentages of HIV symptoms recorded at post delivery visit 1 through to 18 months visit between the two treatment groups for both mothers and infants. A similar pattern was observed for the vital signs for the mothers. The full blood and T-cell counts were similar between the two treatment groups at all the visits for both mothers and infants.

Chapter 5: SAFETY EVALUATION

The safety of vitamin A (freedom from harm or damage resulting from adverse events caused by the use of vitamin A) was assessed by recording vital signs, full blood counts as well as adverse events.

5.1 Vital signs

Table 5.1 shows the descriptive statistics for the vital signs measured at baseline, post-delivery 3, 6, 12 and 18 months visits per treatment group. The column marked baseline subset represents the descriptive statistics at baseline for those patients who attended post-delivery visit 3 months. This subset was taken so that the values from the same patients who attended post-delivery visits can be compared with baseline. The means for all vital signs in the vitamin A group are similar to those in the placebo group at all the visits.

The means for the vital signs did not change markedly from baseline values to the last (post-delivery 18 months) visit in either treatment group.

Table 5.1
Vital signs: Mothers
Population: Safety

Treatment	Variable [unit]	Statistic	Baseline all	Baseline subset	3 months	6 months	12 months	18 months
Vitamin A	SBP [mmHg]	N	152	67	67	58	51	42
		Mean	112.7	112.1	119.9	120.5	115.4	113.3
		SD	12.4	11.6	6.6	7.6	8.4	6.5
		Min	80.0	90.0	95.0	110.0	100.0	100.0
		Median	110.0	110.0	120.0	120.0	110.0	110.0
		Max	150.0	145.0	140.0	155.0	150.0	140.0
	DBP [mmHg]	N	152	67	67	58	51	42
		Mean	65.5	63.8	79.2	79.0	78.1	76.7
		SD	11.9	11.3	6.1	5.5	4.7	4.5
		Min	40.0	40.0	60.0	60.0	70.0	60.0
		Median	70.0	60.0	80.0	80.0	80.0	75.0
		Max	96.0	90.0	95.0	98.0	90.0	88.0
	Heart rate [beats/min]	N	141	64	67	57	51	42
		Mean	75.5	76.1	75.2	75.6	77.7	79.7
		SD	9.3	10.0	3.7	3.5	7.1	6.7
		Min	58.0	58.0	66.0	66.0	62.0	58.0
		Median	75.0	74.0	76.0	76.0	76.0	84.0
		Max	120.0	120.0	84.0	84.0	110.0	90.0
Placebo	SBP [mmHg]	N	150	73	74	70	63	49
		Mean	110.8	109.3	120.9	119.8	117.0	114.4
		SD	10.6	11.3	9.3	9.7	12.5	7.4
		Min	90.0	90.0	100.0	100.0	100.0	100.0
		Median	110.0	110.0	120.0	120.0	120.0	110.0
		Max	150.0	150.0	160.0	160.0	200.0	140.0
	DBP [mmHg]	N	150	73	74	69	63	49
		Mean	63.1	63.5	79.5	78.2	77.1	75.9
		SD	11.2	11.3	6.9	6.1	7.6	6.5
		Min	40.0	40.0	60.0	60.0	50.0	60.0
		Median	60.0	60.0	80.0	80.0	80.0	75.0
		Max	90.0	90.0	100.0	100.0	120.0	95.0
	Heart rate [beats/min]	N	135	66	74	70	63	49
		Mean	75.2	76.4	74.9	75.7	78.9	81.4
		SD	8.7	8.9	4.6	4.8	5.3	7.0
		Min	58.0	58.0	60.0	62.0	66.0	68.0
		Median	74.0	77.0	76.0	76.0	76.0	84.0
		Max	102.0	100.0	84.0	84.0	100.0	110.0

5.2 Full blood counts

Mothers

Full blood counts for mothers in both treatment groups as from baseline to the post-delivery 18 month visit are shown in Table 5.2. All means for the full blood counts in the vitamin A group are similar to those in the placebo group at all visits. The means of all full blood counts did not change markedly from baseline to the post-delivery 18 month visit for either treatment group.

Table 5.2
Full blood counts: Mothers
Population: Safety

Treatment	Variable [unit]	Statistic	Baseline all	Baseline subset	3 months	6 months	12 months	18 months
Vitamin A	Haemoglobin[g/dl]	N	151	65	63	58	50	42
		Mean	11.04	11.09	12.72	13.01	12.92	12.70
		SD	1.26	1.35	1.53	1.21	1.64	1.35
		Min	8.10	8.10	8.30	9.90	7.70	9.10
		Median	11.00	11.00	12.90	13.15	13.00	12.95
		Max	14.10	14.10	17.10	15.90	18.06	15.70
	Haematocrit[L/L]	N	151	65	63	58	50	42
		Mean	0.336	0.338	0.399	0.406	0.401	0.385
		SD	0.035	0.038	0.041	0.039	0.046	0.041
		Min	0.260	0.210	0.290	0.300	0.250	0.280
		Median	0.340	0.340	0.400	0.410	0.400	0.395
		Max	0.420	0.420	0.540	0.490	0.550	0.490
	Red blood cells[10^9cells/litre]	N	150	64	63	58	50	42
		Mean	3.759	3.743	4.606	4.624	4.530	4.390
		SD	0.403	0.438	0.482	0.415	0.532	0.476
		Min	2.700	3.070	3.420	3.770	2.830	3.140
		Median	3.700	3.665	4.580	4.655	4.560	4.445
		Max	5.270	4.710	6.570	5.560	6.220	5.280
	White blood cells[10^9cells/litre]	N	150	64	63	58	50	42
		Mean	6.78	6.58	5.67	5.55	5.34	5.59
		SD	2.02	1.94	2.08	1.62	1.82	1.78
		Min	3.10	3.10	2.50	3.00	2.10	3.10
		Median	6.50	6.65	5.40	5.30	4.85	5.10
		Max	13.60	13.60	14.30	10.90	10.60	10.20
	Lymphocytes[10^9cells/litre]	N	151	65	63	58	50	42
		Mean	1.77	1.74	2.30	2.15	1.89	2.00
		SD	0.61	0.52	0.80	0.65	0.58	0.63
		Min	0.40+	0.80+	1.10	0.70+	1.00	1.00
		Median	1.70	1.80	2.10	2.10	1.80	1.95
		Max	4.20*	3.80*	5.50*	3.60*	3.70*	3.60*
	Neutrophils[10^9cells/litre]	N	151	65	63	58	50	42
		Mean	4.41	4.19	2.89	2.94	3.01	3.12
		SD	1.59	1.51	1.60	1.22	1.43	1.44
		Min	1.60	1.60	0.80	1.20	0.80	1.30
		Median	4.20	4.00	2.60	2.75	2.60	2.60
		Max	9.30	8.02	9.60	6.40	6.30	6.80
	Monocytes[10^9cells/litre]	N	151	65	63	58	50	41
		Mean	0.377	0.380	0.335	0.292	0.315	0.321
		SD	0.147	0.161	0.194	0.090	0.132	0.107
		Min	0.100	0.100	0.110	0.110	0.140	0.140
		Median	0.360	0.370	0.300	0.280	0.280	0.310
		Max	1.090	1.090	1.260	0.560	0.830	0.620
	Eosinophils[10^9cells/litre]	N	150	64	63	58	50	41
		Mean	0.138	0.161	0.203	0.132	0.089	0.117
		SD	0.134	0.170	0.334	0.186	0.081	0.114
		Min	0.000	0.000	0.000	0.000	0.002	0.010
		Median	0.100	0.100	0.100	0.060	0.060	0.080
		Max	1.010	1.010	2.13*	1.160	0.310	0.500
	Thrombocytes[10^9cells/litre]	N	151	65	63	58	50	42
		Mean	265.0	270.3	297.2	291.9	279.8	303.2
		SD	76.9	70.1	76.1	70.1	80.1	71.3
		Min	100.0	125.0	141.0	134.0	79.0	188.0
		Median	250.0	261.0	281.0	287.5	282.0	304.5
		Max	543.0	496.0	513.0	485.0	464.0	507.0

+Values are abnormally low. * Values are abnormally high

Treatment	Variable [unit]	Statistic	Baseline all	Baseline subset	3 months	6 months	12 months	18 months
Placebo	Haemoglobin[g/dl]	N	146	70	70	65	63	47
		Mean	11.01	11.03	12.87	12.76	13.04	12.45
		SD	1.33	1.34	1.26	1.27	1.65	1.57
		Min	5.80	5.80	9.80	9.20	9.90	8.30
		Median	11.10	11.10	12.80	12.70	13.10	12.60
		Max	16.20	16.20	17.60	15.10	20.00	15.50
	Haematocrit [L/L]	N	146	70	70	65	63	47
		Mean	0.335	0.338	0.403	0.396	0.404	0.379
		SD	0.037	0.037	0.037	0.036	0.047	0.042
		Min	0.210	0.210	0.310	0.290	0.320	0.280
		Median	0.340	0.340	0.400	0.400	0.400	0.390
		Max	0.480	0.480	0.560	0.470	0.580	0.450
	Red blood cells[10^9cells/litre]	N	146	70	70	65	63	47
		Mean	3.775	3.781	4.643	4.521	4.575	4.319
		SD	0.370	0.397	0.441	0.422	0.518	0.497
		Min	2.850	2.850	3.550	3.050	3.450	3.090
		Median	3.790	3.795	4.650	4.470	4.510	4.330
		Max	5.200	5.200	6.130	5.470	6.260	5.440
	White blood cells[10^9cells/litre]	N	146	70	70	65	63	47
		Mean	6.76	6.85	5.48	5.51	5.27	5.19
		SD	1.84	1.76	1.74	1.64	1.41	1.51
		Min	2.70	3.20	2.40	2.40	2.50	3.00
		Median	6.50	6.65	5.20	5.40	5.10	4.90
		Max	11.70	11.70	12.10	10.20	9.20	9.80
	Lymphocytes[10^9cells/litre]	N	146	70	70	65	63	47
		Mean	1.74	1.78	2.13	2.02	2.02	1.82
		SD	0.58	0.64	0.76	0.83	0.75	0.65
		Min	0.70	0.70	2.00	0.70	0.80	0.40
		Median	1.70	1.79	2.00	1.90	1.90	1.70
		Max	4.60	4.60	5.10	5.30	4.40	3.50
	Neutrophils[10^9cells/litre]	N	146	70	70	65	63	47
		Mean	4.49	4.55	2.93	3.02	2.82	2.91
		SD	1.54	1.48	1.30	1.04	1.09	1.21
		Min	1.10	2.00	0.80	1.30	1.00	1.10
		Median	4.30	4.40	2.65	3.10	2.70	2.60
		Max	9.80	9.00	7.00	6.20	6.40	6.30
	Monocytes[10^9cells/litre]	N	146	70	70	65	63	47
		Mean	0.362	0.364	0.277	0.288	0.287	0.278
		SD	0.149	0.148	0.108	0.123	0.101	0.101
		Min	0.090	0.090	0.140	0.130	0.130	0.160
		Median	0.310	0.315	0.245	0.250	0.270	0.240
		Max	0.960	0.840	0.750	0.870	0.600	0.700
	Eosinophils[10^9cells/litre]	N	145	70	70	65	63	47
		Mean	0.131	0.128	0.111	0.157	0.106	0.131
		SD	0.128	0.127	0.090	0.340	0.100	0.139
		Min	0.000	0.000	0.010	0.000	0.000	0.000
		Median	0.100	0.100	0.090	0.060	0.070	0.070
		Max	0.630	0.630	0.410	2.560*	0.430	0.560
	Thrombocytes[10^9cells/litre]	N	146	70	70	65	63	47
		Mean	272.4	263.0	292.7	285.9	284.9	308.5
		SD	68.3	60.0	63.8	60.5	68.3	70.8
		Min	130.0	134.0	182.0	177.0	114.0	172.0
		Median	269.0	254.5	294.5	282.0	278.0	300.0
		Max	476.0	406.0	443.0	474.0	502.0	550.0

*Value is abnormally high

Infants

Table 5.3 presents the means for the full blood counts for both vitamin A and placebo groups for infants from post-delivery 3 month to post-delivery 18 months. The means of the full blood counts in the vitamin A group are similar to those in the placebo group. In general, the means of the full blood counts did not change markedly as from post-delivery 3 months to 18 months for either treatment group. In both treatment groups some infants had monocyte values far above the laboratory reference values. It is postulated that the infants may have had unknown infections at the time when the blood was drawn.

Table 5.3
Full blood counts: Infants
Population: Safety

Treatment	Variable [unit]	Statistic	3 months	6 months	12 months	18 months
Vitamin A	Haemoglobin[g/dl]	N	59	59	51	41
		Mean	10.20	10.57	10.85	10.73
		SD	0.91	0.86	1.09	0.98
		Min	7.60	8.10	7.46	8.50
		Median	10.30	10.50	11.00	11.00
		Max	13.70	12.20	12.80	12.20
	Haematocrit[L/L]	N	59	59	51	41
		Mean	0.310	0.322	0.335	0.327
		SD	0.029	0.026	0.028	0.023
		Min	0.250	0.260	0.260	0.270
		Median	0.310	0.320	0.340	0.330
		Max	0.430	0.380	0.400	0.370
	Red blood cells[10^9cells/litre]	N	59	59	51	41
		Mean	3.865	4.341	4.518	4.411
		SD	0.385	0.393	0.371	0.362
		Min	3.120	3.510	3.760	3.730
		Median	3.860	4.310	4.530	4.450
		Max	4.900	5.260	5.310	5.080
	White blood cells[10^9cells/litre]	N	59	59	51	41
		Mean	11.24	10.87	11.00	9.78
		SD	4.55	3.26	4.11	2.80
		Min	5.60	5.00	5.10	4.30
		Median	10.60	10.80	9.50	9.20
		Max	32.60	22.50	23.20	15.10
	Lymphocytes[10^9cells/litre]	N	59	59	51	41
		Mean	6.91	6.72	6.16	5.60
		SD	2.75	2.31	2.18	1.84
		Min	1.80	2.50	2.50	2.10
		Median	6.50	6.20	6.00	5.40
		Max	18.70	12.00	13.50	9.50
	Neutrophils[10^9cells/litre]	N	59	59	51	41
		Mean	2.87	2.88	3.39	2.95
		SD	1.65	1.42	2.15	1.43
		Min	0.60	1.00	0.80	0.40
		Median	2.50	2.50	2.80	2.50
		Max	8.70	9.10	10.80	6.90
	Monocytes[10^9cells/litre]	N	59	59	51	41
		Mean	0.896	0.846	1.066	0.662
		SD	0.552	0.430	1.697	0.379
		Min	0.350	0.250	0.290	0.220
		Median	0.780	0.710	0.680	0.570
		Max	3.880*	2.220*	1.240*	2.530*
	Eosinophils[10^9cells/litre]	N	59	59	51	41
		Mean	0.419	0.309	0.247	0.325
		SD	0.400	3.295	0.237	0.340
		Min	0.010	0.030	0.000	0.020
		Median	0.270	0.200	0.200	0.190
		Max	1.940	1.660	1.170	1.710
	Thrombocytes[10^9cells/litre]	N	59	59	51	41
		Mean	399.7	394.3	384.1	425.2
		SD	140.9	142.3	138.4	157.1
		Min	29.0	85.0	55.0	179.0
		Median	417.0	380.0	384.0	400.0
		Max	841.0	754.0	704.0	904.0

*Values are abnormally high

Treatment	Variable [unit]	Statistic	3 months	6 months	12 months	18 months
Placebo	Haemoglobin[g/dl]	N	63	61	63	48
		Mean	10.12	10.66	10.99	10.91
		SD	1.00	1.16	0.91	1.00
		Min	7.20	7.30	8.60	8.30
		Median	10.20	10.60	11.00	10.95
		Max	12.10	13.20	12.90	13.10
	Haematocrit[L/L]	N	63	61	63	48
		Mean	0.307	0.322	0.335	0.331
		SD	0.031	0.030	0.028	0.028
		Min	0.230	0.240	0.280	0.270
		Median	0.310	0.320	0.330	0.330
		Max	0.400	0.400	0.400	0.380
	Red blood cells[10^9cells/litre]	N	63	61	63	48
		Mean	3.832	4.332	4.532	4.533
		SD	0.463	0.412	0.364	0.392
		Min	2.890	3.350	3.700	3.610
		Median	3.820	4.590	4.540	4.525
		Max	5.280	5.360	5.230	5.370
	White blood cells[10^9cells/litre]	N	63	61	63	48
		Mean	10.26	10.16	10.14	9.97
		SD	3.42	3.18	3.05	3.29
		Min	4.00	4.00	4.90	5.10
		Median	10.10	9.80	9.70	9.50
		Max	19.6	22.30	22.10	23.30
	Lymphocytes[10^9cells/litre]	N	63	61	63	48
		Mean	6.42	6.27	6.05	5.73
		SD	2.19	2.36	2.45	2.05
		Min	2.10	0.80	1.90	2.20
		Median	6.20	6.10	5.80	5.20
		Max	11.40	13.70	15.00	11.60
	Neutrophils[10^9cells/litre]	N	63	61	63	48
		Mean	2.62	2.81	3.08	3.27
		SD	1.45	1.31	1.40	1.37
		Min	0.60	0.20	0.80	1.10
		Median	2.10	2.50	3.00	3.20
		Max	8.00	7.00	9.50	8.30
	Monocytes[10^9cells/litre]	N	63	61	63	48
		Mean	0.772	0.721	0.658	0.630
		SD	0.366	0.365	0.251	0.354
		Min	0.210	0.200	0.320	0.230
		Median	0.660	0.660	0.610	0.545
		Max	2.230*	2.040*	1.550	2.610*
	Eosinophils[10^9cells/litre]	N	63	61	63	48
		Mean	0.305	0.251	0.244	0.295
		SD	0.242	0.205	0.273	0.279
		Min	0.000	0.000	0.020	0.200
		Median	0.210	0.200	0.170	0.220
		Max	1.220	0.950	1.520	1.490
	Thrombocytes[10^9cells/litre]	N	63	61	63	48
		Mean	380.3	372.8	394.9	436.0
		SD	134.0	137.9	126.8	123.6
		Min	54.0	63.0	64.0	211.0
		Median	401.0	368.0	389.0	421.0
		Max	617.0	735.0	756.0	879.0

* Values are abnormally high.

5.3 Abnormal full blood counts: Mothers

Table 5.4 compares the percentages of patients with full blood count values lower than the lower boundary of the normal range for this population from baseline to 18 months visit. Few patients have full blood counts lower than the lower boundary of the normal range for this population in either treatment group at any visit. The percentages of patients with values lower than the normal ranges in vitamin A group are similar to those in the placebo group at all visits and for all variables. The most common variable with values below the normal range was neutrophils followed by white blood cells at all the post-delivery visits for both treatment groups; at baseline the most common were Haemoglobin and Haematocrit.

Table 5.4
Full blood counts lower than the lower boundary of the normal range: Mothers
Population: Safety

Treatment	Variable	Baseline		Baseline subset		3 months		6 months		12 months		18 months	
Vitamin A		n	%	n	%	n	%	n	%	n	%	n	%
			N=151		N=65		N=63		N=58		N=50		N=42
	Haemoglobin	37	24.5	17	26.2	5	7.9	1	1.7	2	4.0	2	4.8
	Haematocrit	43	28.3	20	30.8	2	3.2	1	1.7	1	2.0	3	7.1
					N=64								
	Red blood cells	17	11.3	11	17.2	0	0.0	0	0.0	2	4.0	2	4.8
					N=64								
	White blood cells	8	5.3	6	9.4	12	19.1	11	19.0	12	24.0	9	21.4
	Lymphocytes	8	5.3	3	4.6	0	0.0	2	3.5	0	0.0	0	0.0
	Neutrophils	9	6.0	6	9.2	27	42.9	22	37.9	20	40.0	14	33.3
	Monocytes	6	4.0	4	6.2	6	9.5	7	12.1	6	12.0	3	7.3
					N=64								
	Eosinophils	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Thrombocytes	5	3.3	2	3.1	1	1.6	1	1.7	1	2.0	0	0.0
			N=146		N= 70		N=70		N=65		N=63		N=47
Placebo	Haemoglobin	32	21.2	14	20.0	1	1.4	2	3.1	1	1.6	5	10.6
	Haematocrit	35	23.2	15	21.4	1	1.4	2	3.1	0	0.0	6	12.8
	Red blood cells	9	6.2	5	7.1	0	0.0	1	1.5	0	0.0	2	4.3
	White blood cells	5	3.4	1	1.4	14	20.0	14	21.5	15	23.8	11	23.4
	Lymphocytes	8	5.5	4	5.7	0	0.0	3	4.6	1	1.6	2	4.3
	Neutrophils	5	3.4	1	1.4	30	41.4	19	29.2	23	36.5	19	40.4
	Monocytes	11	7.5	4	5.7	10	14.3	10	15.4	9	14.3	6	12.8
	Eosinophils	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Thrombocytes	6	4.1	2	2.9	0	0.0	0	0.0	1	1.6	0	0.0

5.4 Adverse events (excluding deaths)

Table 5.5 shows the adverse events reported during the study. Only four patients reported adverse events. No patient was prematurely terminated due to adverse events. Study drug

was withdrawn from patient number 76 after she took it for only four non-consecutive days. There was no definite link between the adverse event and the treatment in any of the four patients.

Table 5.5
Adverse events
Population: Safety

Patient number	Treatment	Patient	Adverse Event	Nature	Intensity	Relation to drug	Action taken	Outcome
27	Placebo	Infant	Gastro and flu	Serious	Severe	No	Went to clinic for rehydration	Death
28	Placebo	Mother	Genital ulceration & chicken pox	Serious	Mild	Likely	Concomitant therapy	Improved
76	Vitamin A	Mother	Swelling face after taking the medication	Serious	Moderate	Likely	Study drug withdrawn	Resolved
76*	Vitamin A	Infant	Fits & seizures, Meningitis	Serious				Death

* All information for this infant was reported by the mother two months after delivery. The mother absconded her 1 month visit and later came to the clinic after being traced when the baby was already dead

5.5 Deaths

Information on most of the deaths reported in this study was obtained by the Hospice workers when they traced the patients who did not attend their follow-up visits. Some of the information was obtained from relatives who were at home at the time of tracing. It was difficult to assess the association of the deaths with the study treatment because of the general lack of information on causes of death. Furthermore, it was not possible to establish the age at which most of these infants died. All deaths (of those patients that could be followed) that occurred during the study are listed in Table 5.6. Only 8 patients reported the death of their infants directly to the doctor. According to the information available a total of 26 infants and 1 mother died during the study period. The infant mortality rate obtained based on the available information was 85.8 per 1000 infant

population. In the placebo group, 17 (11.3%) infants died whereas in vitamin A group, 9 (5.9%) infants died. There is no statistically significant difference (p=0.0972). The risk difference is 5.4% with 95% CI (-0.9%; 11.6%). The relative risk of infant mortality is approximately 0.526 (95% CI (0.2421; 1.1427)); that is, infants who were receiving vitamin A had about 0.5 times the risk of death compared to those infants who were receiving placebo.

Table 5.6
Total deaths
Population: Safety

Patient No	Treatment Group	Dead patient	Illness	Action taken	Source of information
16	Vitamin A	Infant			Clinic sister working with the study team provided the information
73	Vitamin A	Infant			Brother gave the information to the Hospice personnel during tracing
76	Vitamin A	Infant	Fits & seizures	Taken to clinic	Patient reported to the doctor
106	Vitamin A	Infant			Aunt gave the information to the Hospice personnel During tracing
163	Vitamin A	Infant			Patient reported to study monitor and she was very sick and did not want to give more information
224	Vitamin A	Infant			Patient phoned study monitor
226	Vitamin A	Infant	Severe oral thrush, splenomegally	Taken to hospital	Patient reported to the doctor
231	Vitamin A	Infant			Patient gave the information to the Hospice personnel during tracing
255	Vitamin A	Infant	Diarrhoea & vomiting	Taken to hospital	Patient reported to the doctor
1	Placebo	Embryo	In utero death		Study doctor saw the patient
9	Placebo	Infant			Patient reported to study monitor and did not want to wait for the doctor
27	Placebo	Infant	Gastro flu	Taken to the clinic	Patient reported to the doctor
28	Placebo	Infant	Genital ulceration and chicken pox	Concomitant therapy	Clinic counsellor working with the study team provided the information
31	Placebo	Infant			Daughter gave the information to the Hospice personnel during tracing
40	Placebo	Infant	Complications of prematurity		Patient reported to the doctor
83	Placebo	Infant			Grandmother gave the information to the Hospice

					personnel during tracing
107	Placebo	Infant			Grandmother gave the information to the Hospice personnel during tracing
108	Placebo	Infant			Grandmother gave the information to the Hospice personnel during tracing
112	Placebo	Infant	Stillbirth		Patient reported to the doctor
124	Placebo	Infant			Brother gave the information to the Hospice personnel during tracing
165	Placebo	Infant			Person found at the house gave the information to the Hospice personnel during tracing
167	Placebo	Mother			Person found at the house gave the information to the Hospice personnel during tracing
181	Placebo	Infant			Sister gave the information to the Hospice personnel during tracing
190	Placebo	Infant			Grandmother gave the information to the Hospice personnel during tracing
200	Placebo	Infant			Sister gave the information to the Hospice personnel during tracing
256	Placebo	Infant	Diarrhoea, vomiting & loss of weight	Taken to clinic	Patient reported to the doctor
281	Placebo	Infant	Found dead in the cot		Patient reported to the doctor

5.6 Summary: Safety

The vital signs and full blood counts for both mothers and infants in the vitamin A group are similar to those in the placebo group at each visit. These results did not change markedly from baseline to post-delivery 18 months in either treatment group. Extreme values obtained in monocytes and eosinophils were checked and the doctors thought that the patients may have had an unknown infection at the time when blood was collected. Only four patients reported adverse events. Furthermore, 26 infants and one mother died during the study. The death rates were approximately 11% in the placebo group and 6% in the vitamin A group. The overall infant mortality rate was 85.8 per 1000 infant population.

Chapter 6: DISCUSSION AND CONCLUSION

6.1 Recruitment of patients

Two thousand five hundred and forty three patients were tested for HIV antibodies from September 1997 up to January 1999. Of these 595 were identified as HIV antibody positive, yielding an HIV prevalence rate of 23.4 %. This prevalence was very similar to the 22.8% prevalence rate obtained for the Free State in the national annual antenatal HIV survey of the Department of Health in 1998.[4] Overall, about 86% of pregnant women approached were willing to have an HIV test. From the beginning of the study (September 1997) up to January 1999 the proportion of those approached for HIV testing and who were willing to be tested did not change markedly.

Nearly 51% (303 patients) of the 595 identified as HIV positive were recruited into the study, representing 75.8% of the planned sample size of 400. The main reason for the low inclusion rate of HIV positive patients was that many patients (27.4% of 595 who were identified as HIV positive) did not come back to receive their test results. Other studies also found that acceptability of HIV testing in some African prenatal testing programs was high but that many infected women did not return for their test result.[40,84,85] The low return rate of HIV infected women in our study may suggest that they perceive themselves at risk of HIV infection. They may have been exposed to high risk situations in the past, i.e. their past sexual behaviour such as multiple sexual partners, extramarital relationships or being involved with an unfaithful regular partner. The low return rate of HIV positive patients may also suggest that they did not want to know their test result and

may also reflect on the quality of counselling received: maybe patients did not really understand that they had to come back and receive their test results.

Although screening was completely voluntary, only 50% of those screened came back to receive their results in the beginning of the study.[86] Possible causes identified at that stage were: a) results were only available once a week at each clinic when the study physician visited the clinic, since the clinic staff did not see this project as part of their job; b) long waiting time at the clinic and c) fear of the unknown.[86] From March 1998, in order to make results more readily available to patients, the clinic staff gave results to the patients irrespective of whether the study physician was available, and from then on about 72% of the patients who volunteered to have an HIV test came back and received their results.[86]

At the beginning of this study resistance to HIV screening was noted among patients despite the assistance of a qualified counsellor and the emphasis on confidentiality of the results. The reason for this resistance may lie in the complex socio-economic and societal roots of the HIV epidemic. If a person is known to be HIV positive, there may be a suspicion of promiscuity, as well as stigmatisation and discrimination associated with the infection within the community. Therefore, the belief that one is better off without knowing one's HIV status is relatively common. To develop more effective programs in this population, studies are needed that will identify barriers to HIV-1 testing and the causes for failure of testing programs. Studies carried out in developing countries have shown that a woman's decision-making process is affected by obstacles, such as travel

requirements, fears of discrimination, loss of marital security and domestic violence.[40,84,87]

6.2 Counselling

HIV pre-test counselling has become the accepted ethical norm in both routine clinical practice and research.[86,87,88] Patients are prepared for the implications of a positive test during pre-test counselling. This is done in an effort to help the individuals arrive at independent decisions, based on understanding and knowledge as to whether or not to give consent to be tested for HIV. However, counselling is expensive (salaries for counselors for many hours) and time consuming since some of the patients are not yet aware of what HIV and AIDS are. Cartoux *et al* indicated that the mean duration of the individual pre-test and post-test counselling sessions was 15 and 26 minutes, respectively.[84] Jones *et al* noted that consent to HIV testing was twice as likely if pre-test counselling lasted longer than 5 minutes.[89] In our study, the willingness of patients to give consent also depended in part on the skills of the counsellor. Some studies observed that the length of time spent counselling and the individual counsellor involved are the strongest predictors of testing acceptability.[85,88]

It remains very important to emphasize confidentiality of the patient's results during pre-test counselling. In this study pre-test counselling was organized in group sessions due to manpower constraints. Cartoux *et al* found that group pre-test counselling reduced the number of resource persons needed.[84] In our experience, group counselling seemed to

help patients open up, as some patients within the group came from families affected by HIV and were willing to talk about it.

Post-test counselling was done on an individual basis. Some patients became very anxious to get their result, while others did not want to know it. Many of the patients went through all the phases of grief (denial, anger, depression, bargaining and acceptance) after being told that they were sero-positive. Very few questions about the disease were asked during post-test counselling. This fact may indicate that patients received sufficient information during pre-test counselling. On the other hand patients were possibly still in a state of disbelief at that stage and it was important that the study personnel were open to questions at a later stage. This need was confirmed by 39.6% of the 91 trial participants interviewed in the consent study after a mean period of 1 year of participation in the trial who stated that they still had questions regarding HIV and 55.8% felt that they still did not know enough about HIV.[90]

6.3 Ethical issues

Several ethical issues had to be addressed in the planning of this study. HIV transmission through breast-feeding has been documented in several studies.[30,32,33,34] Breast-feeding by HIV positive mothers, therefore, poses an important dilemma: particularly in Africa where alternative infant feeding methods risk millions of infant lives since many mothers cannot afford the milk formulas and access to clean water is limited in many areas. Estimates of the additional risk of HIV infection through breast-feeding range from 7% to 22 %.[22,23,27,91] We followed the consensus statement of the World Health Organization

(WHO)/UNICEF which advise artificial feeding even in developing countries provided formulas and clean water are available and safely used.[10] However, we remained unsure about whether these conditions applied in our situation. There are tremendous societal pressures for women to breast-feed in Africa. Women who choose to formula feed face the risk of being ostracized because it may be seen as a sign that they are HIV infected.[20] Furthermore it was difficult for the mothers to make a decision on breast-feeding since infant formula was not provided free to the study patients. In our setting communication and cross-cultural constraints also complicated giving advice on this subject. Only 31.9% in the vitamin A group and 22.4% in the placebo group eventually breast-fed their infants in this study. However, if breast-feeding is to be substituted by formula feeding in HIV-infected women in the developing world, it is essential that clean water is readily available, formula feeds are affordable, social support networks exist for women who use formula and treatment of diarrhoeal diseases is freely available.

The second ethical dilemma was that of using placebo as control treatment in this study. When the study started, no conclusive evidence regarding the effect of Vitamin A on vertical HIV transmission was available and therefore it was decided that a placebo group could ethically be included. However, while our study was being conducted other studies may have been completed and their results may have led to the discontinuation of the placebo arm of our study. In the event, no similar studies were completed while this study was still ongoing. The placebo arm allowed us to best judge the efficacy of the intervention. The use of historical transmission rates as comparison rates would have led to spurious conclusions since vertical transmission is influenced by many factors such as

maternal viral load, breast-feeding rates and cesarean section rates.[70,92] As these factors change over time, vertical transmission rates also change depending on which factors change and to what extent. The results of the present study are a case in point: the relatively lower transmission rate in the vitamin A arm of the study (about 19.2%) alone when compared to published transmission rates could have been interpreted as evidence of the efficacy of vitamin A. Furthermore, the placebo arm was justifiable because placebo treatment represented the 'standard of care' in South Africa at the time. No anti-retroviral therapies were routinely available.

6.4 Baseline characteristics

Three hundred and three patients were included in the study with 152 randomly allocated to the vitamin A group and 151 to the placebo group. Nearly 56% of the study participants lived in informal housing at recruitment. More than 60% of the patients in both treatment groups were black and Sotho speaking. On average the patients were recruited when they were about 27 weeks pregnant. The mean age in both treatment groups was approximately 26 years.

The study patients were in good health based on physical examination. The mean weight of these women at baseline was 66.1 kg and 64.6 kg in the vitamin A and placebo groups respectively. At the last visit the mean weight was still above 60kg for both treatment groups. At recruitment, 42.7% and 39.9% of patients in vitamin A and placebo group respectively had CD4 counts below 0.390×10^9/l (lower limit of the normal range for this population)[82] but only 14.0% and 8.1% (Table 3.17) were below 0.200×10^9/l (an AIDS

defining criterion) in vitamin A and placebo groups respectively. At the last visit (when infant was 18 months old) 54.8% and 43.5% of patients in vitamin A and placebo groups respectively had CD4 counts less than $0.390x10^9$/l but only 19.1% and 13.0% had CD4 counts less than $0.200x10^9$/l in the respective groups. These percentages indicate that the patients remained relatively healthy throughout the study.

Dannhauser *et al* have shown that HIV/AIDS patients from this population are malnourished and had insufficient intake of micronutrients such as vitamin A, D, C and B_6.[50] Van Staden *et al*[51] found that HIV/AIDS patients from the Free State had low p-retinol levels which were not associated with the degree of immune deterioration. The same group found that there was no strong link between disease progression and nutritional imbalances. This finding may explain why our study patients appeared well-nourished and in good clinical condition. Alternatively, these patients could have been eating a balanced diet since they were pregnant and (in some cases) later lactating mothers. Although no patients had any AIDS related symptoms at entry to the study, 21 and 12 women had CD4 counts$<0.200x10^9$/l (an AIDS defining criterion) in the vitamin A and placebo groups respectively.

Demographic data, HIV symptoms, and vital sign variables as well as full blood and T-cell counts were similar between the two treatment groups at recruitment.

6.5 Follow-up

Eighty five percent of patients included in the study attended their antenatal clinic follow-up dates. The main follow-up problem occurred when the patients transferred from the antenatal clinic to the Immunology clinic where post-natal visits were done. A total of 191 patients (63% of all the participants) missed one or more visits and had to be traced. Seventy three percent of those who missed appointments did so in the postnatal phase and in particular the first post-natal visit (56%). Nearly 46% and 38% of patients in the vitamin A and placebo groups respectively never attended any post-delivery visit. The reason for this non-attendance may be that patients had to move to a different clinic from the one they had attended antenatally.

Hennekens et al noted that the longer the research observation period the more difficult it is to achieve complete follow-up because people are more likely to move or to change jobs.[93] Nearly 47% of 191 non-attendees could not be traced because their address did not exist or no such woman was known at that address. This problem may be due to the fact that about 56% of study participants indicated that they stayed in informal housing that can be easily demolished and moved to another location. These informal settlements have no formal planning and an individual decides the house number he/she wants. As a result, there may be more than one house with the same number in the same informal settlement. This numbering makes it difficult to locate the patient's address. In addition, even when traced, patients may have denied that they are the trial participants because of fear of stigma or domestic violence in case the partner may hear about her HIV status.

About 25% of the non-attendees (191) were visited more than once in order to obtain information on their whereabouts, due to houses being locked or no one available who could give information about the patient at the time of tracing. Care was taken throughout to maintain patient confidentiality.

A nominal fee to cover transport cost was paid for each post-natal visit in order to eliminate lack of transport as a reason for non-attendance. The use of Hospice volunteers, as well as the employment of a research assistant to specifically help with patient tracing, improved the follow-up rates somewhat. However, the number of patients who attended decreased consistently after the first post-delivery visit at one month to the 18 month visit in both treatment groups with only 91 (42 in vitamin A and 49 in placebo) patients attending the last follow-up visit. The extent of non-attendance experienced in this study clearly demonstrates that studies requiring HIV testing and regular follow-up in this population need to be carefully planned, taking into account the complexities of the disease and corresponding societal issues.

The poor adherence to follow-up visits experienced in this study may be due to various factors. Antenatal visits are seen as routine by patients, but regular post-natal visits may need an explanation at home.[86] The fact that some patients gave non-existing addresses and incorrect names may indicate that they did not want their HIV status to be known even by their families. From the difficulty in tracing of these patients it was clear that this population is very mobile, which makes it difficult to trace patients who fail to come for their appointments. Furthermore, it may have been difficult for them to come for follow-

up.[86] In other cases it was not clear whether patients did not return for follow-up because they were no longer interested in the study, since 10.5% of non-attendees traced, promised to come to the clinic but did not. If an infant died, the mother may have assumed that it was unnecessary to continue clinic visits, although the importance of follow-up, even if the baby died, was stressed during recruitment. Other patients may have come from neighbouring countries to use South African medical facilities covertly and they may be the ones who perhaps gave incorrect names and addresses.

From the large number of patients who were non-attendees at some stage during the trial, it is clear that a trial of this nature in this population should have sufficient infrastructure to trace non-attendees on a regular basis and compensate patients for incidental expenses such as transport costs to increase attendance. Participants had agreed that they were going to come for follow-up until the infant was 18 months old. This was one of the major criteria for inclusion in the study. However, this may indicate that at times patients agree to take part in a study half-heartedly or they might have been keen to get some treatment. If this is the case, then researchers must be prepared to face these frustrations more often. In Gauteng where mothers are given nevirapine, the researchers cited mothers not bringing babies back at the clinics for HIV testing as the major problem they are facing.[94]

6.6 Exclusion from statistical analysis: Assessment of possible bias

One hundred and fifty eight patients had a conclusive infant HIV test result (ITT population) with 73 in the vitamin A group and 85 in the placebo group. A total of 104

patients had a conclusive infant HIV test result when the baby was 3 months old (PP population). In Durban, Coutsoudis *et al* had conclusive infant HIV test result at 3 months for 69% of the 728 women enrolled.[58] In our study, patients without a conclusive infant HIV test result (non-attendees) were excluded from the ITT analysis. In order to assess whether there were any systematic differences between patients included in the primary analysis (ITT population) and patients who were not, patient characteristics measured at recruitment were compared since any such differences could bias the study results. In the event there was no statistically significant difference in demographic data, medical history, vital signs, physical examination, race, language, obstetrical and laboratory data between patients in ITT population and those not in ITT population. Therefore, there was no statistically significant difference between attendees and non-attendees at baseline.

Research has shown that failure to obtain outcome data on every subject or collecting it on a greater proportion of individuals in either treatment or control group, is a major source of potential bias and could render the results of a study uninterpretable.[95,96] For example, Hira et al cited an HIV vertical transmission rate of 39% yet 47% of the cohort had been lost to follow-up and those remaining may have been ill.[97] However, the percentage of participants lost to follow-up (at each visit) in our study was evenly distributed among both vitamin A and placebo groups. Therefore the risk of bias was probably small and the study findings may not have been threatened.

6.7 Efficacy of vitamin A supplementation

The vertical HIV transmission rates obtained in this study were 22.2 % and 19.2 % in the placebo and vitamin A groups, respectively. There was no statistically significant

difference between these two rates (p=0.76) for the ITT population. The same conclusion was found for the PP population. These results indicate that vitamin A was not effective in reducing the transmission rate of HIV-1 from mother-to-child in this study population. These results also confirm the necessity of the placebo arm as efficacy of vitamin A might have been presumed if the data were compared with the historical transmission rates of 25% to 45% [20,97,98] obtained in other studies in Sub-Saharan Africa.[97]

The reduction of sample size (from 400 to 303) in this study may have reduced the power to detect any differences between the two groups. Our results are, however, consistent with what was found in a study carried out in Durban on the effect of vitamin A supplementation on early mother-to-child HIV-1 transmission,[58] where the mother-to-child transmission in the intervention group and placebo arm were similar at 1 day after birth, at 1 month of age and at three months (20.3% and 22.3% in vitamin A and placebo groups respectively) of age. The transmission rates obtained in the Durban study at three months of age are strikingly similar to those obtained in our study for the respective treatment groups.

The observed lack of efficacy is unlikely to be due to a failure of randomisation at recruitment. At baseline the characteristics of the women in the two groups were similar. These characteristics were also similar for those women in the ITT population and those who were not. In this case the lack of efficacy may be due to the fact that the patients were not vitamin A deficient (baseline levels were not measured in this study). The mean vitamin A levels observed in 1995 for HIV positive male and female patients at the

Pelonomi hospital, Bloemfontein by Dannhauser et al was 671.0 μg RE with 58% of patients having less than the 67% of the required dietary allowance[50]. It can, however, not be concluded that the present study participants (pregnant women) were similarly vitamin A deficient since pregnant women may be more likely to eat a balanced diet than the general population. Semba *et al*[46] observed that women with low serum retinol levels at baseline had higher transmission rates than those with higher serum retinol levels. Alternatively the patients may not have taken the tablets (non-compliance to treatment) in phase I of this study. Non-compliance to treatment is unlikely since there is an equal number of late converters in the vitamin A and placebo groups and we are sure that the patients were taking the medication in the post-natal phase of the study.

The lack of a strong effect of vitamin A supplementation on reducing mother-to-child HIV-1 transmission in this clinical study suggests that vitamin A serum concentrations may be markers of the stage of HIV-1 disease progression or intermittent infections rather than being causally related to vertical transmission of HIV-1. Retinol is known to be decreased by the acute phase response to infection, even in the presence of adequate liver stores of vitamin A .[46,58,77,99] It is unlikely that the lack of effect was related to insufficient vitamin A supplementation as relatively high doses (these were considered the safest doses not associated with teratogenicity[100]) of vitamin A were used in this study.

Previous studies have identified the multi-factorial nature of perinatal transmission whereby high plasma viral load is an important determinant of vertical

transmission.[70,92,101] It would have been ideal to measure the viral load for these women; unfortunately this was not done due to financial constraints. The low (lower than expected) transmission rate in the placebo group and lack of efficacy could possibly have been explained by the viral load in these women.

Sera from expectant mothers were tested for HIV-1 antibodies using two commercial enzyme linked immunosorbent assays (ELISAs) in parallel (Vironostika HIV Uni-FormII Ag/Ab and Behring Enzygnost HIV Integral).[102,103] This method is the recommended diagnostic stategy for HIV infection in South Africa (for patients drawn from populations where sero-prevalence is greater than 10%).[104] If a patient requested a retest, blood was drawn and re-tested before she was recruited in the study. The tests are sensitive and specific (Behring test has a 100% sensitivity and a specificity of 99.3% to 99.95% on initial test and 99.7% to 100% on re-test, whereas Vironostika has a specificity of 99.96% after repeat testing)[102,103] and the PPV is >90% in this population,[105] where the HIV prevalence among women attending antenatal clinics was 22.8% during the recruitment period.[4] We are confident that the patients in this study are in fact HIV positive despite the lack of vitamin A efficacy and the low transmission rate in the placebo group.

The results of other studies offer intriguing suggestions that vitamin A supplementation, although not able to reduce vertical transmission, may be of some benefit for other pregnancy outcomes.[58] Semba *et al* in Malawi, reported a reduction in the incidence of low birth weight deliveries among HIV-infected women supplemented with vitamin A compared with those in the placebo group.[46] Unfortunately infant birth weights were not

measured in our study since mothers did not bring the baby health cards to the post-natal follow-up visits.

The results from a trial in South Africa among children born to HIV infected mothers showed positive effects of vitamin A supplementation which resulted in approximately 50% reduction in diarrhoeal morbidity among HIV infected children [52]. Coutsoudis and colleagues in South Africa found that maternal vitamin A supplements significantly reduced the incidence of pre-term deliveries from 17.4% in the mothers on placebo to 11.4% in the treatment group.[58] The percentages of pre-term deliveries obtained in our study were 14.9% and 20.0% in vitamin A and placebo groups respectively. However these percentages did not differ statistically significantly (p=0.4161). Coutsoudis *et al* found that vitamin A supplementation to a population of HIV-infected pregnant women, many of whom had low vitamin A levels, was associated with reduced mother-to-child transmission of HIV in pre-term babies although the sample size was small.[58] In our study we observed a non-statistically significant association of vitamin A with reduction in infant mortality which may be medically important.

At baseline the mean CD4 counts for the Durban study participants were similar to those obtained for our study participants. The means were 0.471×10^9/l in the vitamin A group and 0.459×10^9/l in the placebo group.[58] These mean CD4 counts indicate that the patients who participated in the Durban study were also still in good clinical condition at recruitment.

The transmission rate of 22.2% found in the placebo group of this study is within the range of the transmission rates (20% to 45%) reported in other parts of Africa, although at the lower end of the range. [12,13,98] This transmission rate is lower than the rate reported for Rwanda (25.7%), [106] Zambia (39%)[97] and Durban (34%) for 1996 (where it was found that patients whose haemoglobin values were below 10g/dl during pregnancy were at increased risk of transmission),[98] but is almost identical to the rate of 22.3% reported for the Durban study in 1999.[58] The fact that the mothers in this study were asymptomatic throughout the study and less than 40% breast-fed their infants could account for the lower transmission rate than that obtained in Rwanda where mothers with severe immosuppression (CD4/CD8<0.5) were 2.9 times more likely to transmit HIV-1 infection to their infants.[106] In Zambia 53% of the women were symptomatic and that may explain the high perinatal transmission rate.[97]

In the present study, very few patients had HIV-related symptoms (as assessed by medical history and physical examinations variables), at all the visits. There was no statistically significant difference in HIV-related symptoms, T-cell and full blood counts between the two treatment groups at all the visits for both mothers and infants in both safety and ITT populations. Therefore the results of this study indicate that maternal vitamin A supplementation my be helpful in reducing infant mortality but not vertical HIV transmission.

6.8 Vertical transmission preventative programs

In order to reduce the vertical transmission of HIV, the implementation of large-scale preventative programs for HIV positive patients attending antenatal clinics may eventually be considered by the South African government. In the Free State, such programs are currently being planned by the Free State Provincial Health Authorities. Two pilot sites investigating nevirapine are currently underway. The use of nevirapine in Free State antenatal services is expected shortly. However, our study has shown that the infrastructure necessary for such preventative programs does not yet exist.

The associated health services costs of establishing the required infrastructure clearly needs to be factored into cost requirements for these preventative programs. These costs include the provision of adequate resources for pre and post-test counselling. Counselling models are needed that move beyond the individual to the family and wider community to ensure the development of sustainable support for people with HIV and to decrease discrimination. There is also a need for the provision of free formula for the infants whose mothers are HIV infected. This study has helped to establish some infrastructure and expertise for programs aimed at preventing vertical HIV transmission in the Bloemfontein area. Although this study had its own staff, such a project places an extra workload on the normal clinic staff. Cartoux *et al* also noted that incorporating voluntary counselling and HIV testing in existing antenatal clinic services clinic staff will be inadequate,[84] therefore the costs of hiring additional clinic staff must be considered. In our experience, the project staff furthermore had to perform duties not strictly linked to

the project. This indicates that there is need for more support staff in the clinics if these programs are to be implemented successfully.

6.9 Infant mortality

Only 58 infants were seen at one month in each group. Nearly 60% of 75 and 67% of 73 infants were not breast-fed in the vitamin A and placebo groups, respectively. Thus most infants were not breast-fed; this fact and the lack of HIV data for 1 month may explain why we have few late converters. Nine infants died in the vitamin A group and 17 in the placebo group. These figures yield death rates of 11.3% and 5.9% in the placebo and vitamin A groups respectively (p=0.0972). The relative risk of infant mortality was about 0.53 (95% CI: 0.24 to 1.14) for infants in the vitamin A group compared to that in the placebo group. A study done in Tanzania found that vitamin A supplementation resulted in a 49% reduction in mortality (RR 0.51; 95% CI: 0.29 to 0.90).[54] Another study carried out in Durban South Africa, also found that vitamin A supplements resulted in approximately 50% reduction in diarrheal morbidity among HIV-infected children.[52] In a meta-analysis of eight community-based trials that were carried out among largely uninfected children, vitamin A resulted in a 30% reduction in mortality.[103] In two of these eight studies, large doses of vitamin A had no effect on total mortality and the protective effects in the other six studies ranged from 23 to 54%.[107] This variability may be explained by differences across communities in the prevalence of vitamin A deficiency and other nutritional deficiencies that affect the absorption of vitamin A.

Only 4 patients reported adverse events and there was no definite link between the adverse events and the treatment in any of the four patients.

6.10 Conclusion

The problems experienced in this study clearly demonstrate that all studies requiring HIV testing and regular follow-up of patients in the community must be carefully planned, and with due regard of the situation and values of the community in which the study is planned. Conducting a trial aimed at preventing vertical HIV transmission is fraught with problems, highlighting the preparatory work that needs to be done if we are to successfully implement preventive programs.

This study established the baseline transmission rate (21.2%) for Bloemfontein. The observed reduction in infant mortality of 47% although not statistically significant, agrees with findings of earlier studies and therefore is encouraging. Finally, vitamin A supplementation, an affordable intervention, does not appear to be effective in reducing overall mother-to-child transmission of HIV-1 in this population; however its potential effect on the immune system for HIV infected people still needs to be investigated.

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APPENDIX 1

Published article and one article in press arising from the study

The Southern African Journal of Epidemiology and Infection 2000; 15 (1): 19-22

Lessons learned in establishing a randomised controlled trial to investigate the effect of vitamin A on vertical transmission of HIV-1

P Chikobvu, WJ Steinberg, G Joubert, JI Viljoen, M Coetzee, J Kriel, E van der Ryst

Problems encountered in setting up a randomised controlled trial to investigate the effect of vitamin A in reducing vertical transmission of HIV-1 are described, and practical solutions, are suggested. The trial involved HIV-positive pregnant women attending the antenatal clinics of the Universitas and Pelonomi hospitals, as well as the Mangaung University Community Partnership Programme clinic in Bloemfontein. Routine HIV screening is done at one of the clinics, whereas voluntary screening was initiated at the two other clinics. Subjects were requested to participate in the trial during post-test counselling, and randomised into either the treatment or placebo arm of the study. Follow-up is continued until the baby is 18 months old. Five hundred and ninety five of the 2 543 patients screened from September 1997 up to January 1999 were HIV-seropositive. Approximately 27% of them did not return to receive their test results, and of those who returned, 70.1% gave consent for inclusion in the study. The most frequent reasons for non-participation were denial and unwillingness to join the study. The running of a trial of this nature is fraught with problems, the most important being loss to follow-up. Up to now 61.4% of those included in the study did not attend their follow-up visits regularly. Furthermore, this study highlights the potential problems that may be encountered with the large-scale introduction of measures to prevent vertical transmission. Innovative measures, such as the use of non-government organisations, eg. Hospice, to help with the tracing of patients, can help solve these problems.

Introduction

Vertical transmission is the primary means by which young children become infected with human immunodeficiency virus type 1 (HIV-1).[1-3] Transmission can take place either in utero, during labour and delivery, or post-natally through breast feeding.[1,3-6] However, the relative contribution of each of these routes remains poorly quantified. Reported rates of mother-to-child HIV transmission differ significantly between developed and developing countries. The overall HIV transmission rates have been reported as ranging from 20%-40% in Africa in contrast to 10%-20% in the USA and Europe.[2,7-10] The results of the Aids Clinical Trials Group (ACTG) 076 trial, released in early 1994, showed that zidovudine (or AZT) administered to HIV-infected pregnant women and their newborns reduced the transmission rate by about two-thirds.[3,11] A study carried out in Thailand demonstrated that a short course of twice daily zidovudine used from 36 weeks gestation until delivery reduced the risk of vertical transmission of HIV-1 by approximately one-half.[12] However, the implementation of these strategies in Africa is hampered by financial constraints.[13,14] Vertical transmission of HIV, therefore, remains a serious problem for many developing countries, particularly in Africa, where the majority of HIV-positive mothers can not afford AZT.[13,14] A relatively cheaper method of reducing vertical transmission is, therefore, needed.

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Semba and co-workers demonstrated that vitamin A levels of mothers who transmitted HIV to their infants were significantly lower than those who did not transmit the disease,[15] and that the degree of vitamin A deficiency was significantly related to mortality of the infants.[16] Coutsoudis *et al*, however, found that vitamin A supplementation during the third trimester and at delivery did not lower transmission rates, but that women receiving vitamin A supplementation were less likely to have a preterm delivery, and among the preterm babies, babies of supplemented mothers were less likely to be infected than babies of mothers in the placebo group.[17] In a study investigating the effect of vitamin A supplementation to children aged 6 months to 5 years, it was found that HIV-positive children receiving vitamin A had lower mortality rates than children in the placebo group.[18] A double-blind randomised controlled trial to determine the effect of oral administration of vitamin A to HIV-positive pregnant women, subsequently lactating or non-lactating mothers and their infants on the vertical transmission of HIV-1 was set up in Bloemfontein, South Africa. Participants were recruited from women attending the antenatal clinics at Universitas and Pelonomi hospitals and the Mangaung University Community Partnership Program (MUCPP) antenatal clinic. This trial is an interdepartmental project, involving clinical departments (Obstetrics and Gynaecology, Paediatrics and their clinical personnel), laboratories (Virology, Haematology and laboratory technicians) and Biostatistics. Ethics committee approval was obtained from the Ethics Committee, Faculty of Health Sciences, University of the Orange Free State in 1996. In this paper we describe problems experienced in setting up the trial, and suggest practical solutions.

Materials and methods

Screening for HIV antibodies

Routine screening (including pre- and post-test counsel-

ling)[19] for the presence of HIV antibodies is done at the antenatal clinic of Universitas Hospital. At the other two sites used in this study no routine screening existed. To identify possible participants for the study, voluntary HIV screening of patients attending these clinics was started in September 1997. The same study doctor screened all patients at their first antenatal visit. Voluntary patient screening was coupled with pre- and post-test counselling. Pre-test counselling was done in groups and a prevalence rate of 20%[20] was used. The patients were asked to give written consent for HIV testing and to come back to get their results after one week. Sera were tested for the presence of HIV-1 antibodies using two commercial enzyme-linked immunosorbent assays (ELISAs), the Vironostika HIV-1 and -2 (Organon-Teknika, South Africa) and Behring Enzygnost HIV-1 and -2 PLUS (Behringwerke, Marburg, Germany) test kits.

Recruitment into the study

During the counselling process patients were informed of the study and the risk of giving birth to an infected baby. During post-test counselling patients were asked whether they were willing to participate in the study. Patients who gave consent were included in the study at their second antenatal visit if they were between 20 and 36 weeks pregnant, had the ability to comprehend, were able to come for regular follow-up and gave written informed consent. Those patients who were willing to join the study but were still very early in pregnancy were asked to come back when their pregnancy was at 26 weeks. Participants were randomly allocated to receive vitamin A or placebo, and the infants received active or placebo treatment depending on the randomised treatment of their mothers. Three hundred and three women were included in the trial. Recruitment stopped in January 1999.

Study visits

Patients were seen at two-monthly intervals in the antenatal phase, and are being seen in the post-natal phase at one month and then at three-monthly intervals until the baby is 18 months old. Patients received 5 000 IU/day of vitamin A antenatally. Mothers were given 300 000 IU of vitamin A at the one month post delivery visit and 200 000 IU at each of the subsequent visits. Infants received liquid vitamin A orally, 50 000 IU at 1 and 3 months, 100 000 IU at 6 and 9 months and 200 000 IU in conjunction with vitamin E as an antioxidant at 12 and 15 months of age. Infants in the placebo arm received an equivalent volume of distilled water. At each visit, each patient receives an appointment card listing the date, day and time of her next clinic visit. For postnatal visits patients are reimbursed a nominal fee to cover transport costs. If during the antenatal phase it was expected that the woman would deliver before the next visit, she was given a postnatal clinic appointment. Postnatal visits are at different clinics from the antenatal clinics, but were also located at Pelonomi and Universitas hospitals.

Non-attendees

A research assistant was employed for a three-month period to trace non-attendees. From February 1999 field workers of Bloemfontein Hospice have been following up non-attendees on a regular basis. If a women missed one appointment she is encouraged to continue with the trial. If she missed two or more appointments she is asked to return to the clinic for a withdrawal visit.

Results

HIV antibody screening and recruitment

The proportion of those approached for HIV testing who were willing to be tested did not change markedly during the recruitment period. In general, about 83% of those approached each month were willing to have an HIV test. Two thousand nine hundred and forty nine women were counselled, and 2 543 were screened from September 1997 up to January 1999. Of these, 595 were identified as HIV antibody positive, yielding a prevalence rate of 23.4% which is similar to the 22.8% obtained for the Free State in the national annual antenatal HIV survey of the Department of Health in 1998.[21] Three hundred and three women, thus 50.9% of those identified as positive, were recruited into the study. Reasons for the low inclusion rate of positive patients are given in Table 1. The largest percentage of non-participation was due to patients not returning for their test results. Although voluntary screening is done, only 50% of those screened came back to receive their results in the beginning of the study. Causes identified at that stage were: a) results were only available once a week at each clinic when the study doctor visited the clinic, since the clinic staff did not see this as part of their job; b) long waiting time at the clinic and c) fear of the unknown. To make results more readily available to patients, the clinic staff gave results and about 72% of the patients who volunteered to have an HIV test subsequently received the results.

Table 1: **Inclusion into the study**

HIV-positive patients identified	553	
Recruited into study	273	(49.4%)
Did not return for results	157	(28.4%)
Unwilling to participate	65	(11.7%)
Did not fulfil inclusion criteria	14	(2.0%)
Denial of HIV seropositivity	45	(8.1%)
Would rather visit sangoma	2	(0.4%)

Non-attendees

Up to the end of 1999, 186 women (61.4% of all participants) have missed one or more appointment, and had to be traced by the research assistant or Hospice field workers. Thirty four of these women (18.3%) had given addresses which do not exist. Of the 152 addresses which could be found, the woman was not known or no longer staying at that address in 71 cases (46.7%). In only 12 cases a new address could be obtained for the woman.

Reasons given for non-attendance were generally vague, such as 'I forgot', 'no reason' or 'no longer interested'. However, one woman and two babies had died. Sixty-five women were traced and came back to the clinic. Of these, 50 (26.9% of the 186 non-attendees) continued in the trial and the other 15 had a withdrawal visit since they had missed two or more visits or no longer wanted to continue.

The majority (72.6%) of those who missed appointments did so in the postnatal phase, and in particular the first postnatal visit (57.0%). For 24.2% of the non-attendees the field

workers had to do one or more visit to obtain information.

Discussion

The problems experienced in this study clearly demonstrate that all studies requiring HIV testing and regular follow-up must be carefully planned, taking into account the circumstances and values of the community in which the study is planned. Resistance to HIV screening was noted among patients despite the assistance of a qualified counsellor and the emphasis on confidentiality of the results.

HIV pretest counselling has become the accepted ethical norm in both routine clinical practice and research.[22] However, counselling is expensive and time consuming since some of the patients are not yet aware of what HIV and AIDS are. Jones *et al* noted that consent to HIV testing was twice as likely if pretest counselling lasted longer than five minutes.[23] In this study pretest counselling was organised in group sessions due to manpower constraints. In our experience, group counselling seemed to help patients open up, as some patients within the group may come from families affected by HIV and are willing to talk about it.

Post-test counselling was done on an individual basis. Some patients became very anxious to get their results, while others did not want to hear it. Very few questions about the disease were asked during post-test counselling. Patients may still be in a state of shock at this stage and it is important that the study personnel are open to questions at a later stage.

The poor attendance for follow-up visits experienced in this study was due to various reasons. More than half of the non-attendance occurred between the antenatal phase and the postnatal phase. For postnatal visits patients had to move to a different clinic from the one they had attended as antenatal clinic. Antenatal visits are routine but postnatal visits in that frequency are not routine, and require an explanation at home. From the tracing of non-attendees it was also clear that this population is very mobile, which makes it difficult to trace women who fail to come for their appointments, and it may be difficult for them to come for follow-up. Some patients deliberately gave incorrect addresses, probably because they fear that their family may be informed about their disease. From the large number of women who were non-attendees at some stage during the trial, it is clear that a trial of this nature should have sufficient infrastructure to trace non-attendees on a regular basis, and employ incentives such as some fee to increase attendance.

Several ethical issues had to be addressed in the planning of this study. HIV transmission through breast-feeding has been documented in several studies.[4,5,24-28] Breast-feeding by HIV-positive mothers, therefore, poses an important dilemma, particularly in Africa where alternative infant feeding choices risks millions of infant lives that are saved each year by breast-feeding, since some mothers do not have access to tap water, electricity and some can not afford the formulas. Estimates of the additional risk of HIV infection through breast-feeding range from 7% to 22%.[3-6] In our study, infant formula is not provided free to study participants. We are presently following the consensus statement of World Health Organization (WHO)/UNICEF which advises artificial feeds even in developing countries provided these are available and safely used.[29] However, we remain unsure about the applicability in our situation. Recent findings suggest that babies receiving exclusive breast-feeding until age 3 months have a significantly lower risk of transmission than babies receiving mixed feeding, and a similar risk to those receiving no breast-feeding. In our setting communication and cross-cultural constraints also complicate giving advice on this subject. The second ethical dilemma is that of using a placebo arm. When the study started, no conclusive evidence regarding the effect of vitamin A on vertical transmission was known, and antenatal women were not routinely receiving any medication aimed at reducing the transmission. It was therefore decided that a placebo group could ethically be included. However, several other studies may soon be completed and their results may lead to the discontinuation of the placebo arm.

In order to reduce the vertical transmission of HIV, the implementation of large-scale preventative programmes for HIV-positive patients attending antenatal clinics may eventually be considered by the South African government. Our study has shown that the infrastructure necessary for such preventive programmes does not yet exist. This study has helped to establish some infrastructure and expertise for programmes aimed at preventing HIV transmission. Although the project has its own staff, such a project places an extra load on the clinic staff. In return, project staff have to perform duties not strictly linked to the project. This resulted in maximum co-operation between clinic and project staff. A strong point of the project is the good interdepartmental cooperation.

In conclusion, the running of a trial aimed at preventing vertical HIV transmission is fraught with problems, highlighting the preparatory work that needs to be done if we are to successfully implement preventive programmes.

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Corrections to the table in the manuscript

Table 1: **Inclusion in the study**

HIV- positive identified	595
Recruited in the study	303 (50.9%)
Did not return for results	163 (27.4%)
Unwilling to participate	67 (11.3%)
Did not fulfil the inclusion criteria	14 (2.4%)
Denial of HIV seropositivity	46 (7.7%)
Would rather visit sangoma	2 (0.3%)

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RE: 01/0444: "Consent for Participation in the Bloemfontein Vitamin A Trial: How Informed and Voluntary?

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CONSENT FOR PARTICIPATION IN THE BLOEMFONTEIN VITAMIN A TRIAL: HOW INFORMED AND VOLUNTARY?

Running title: consent for trial

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Abstract

Objective: This study investigated whether the consent for HIV testing and subsequent participation in the Bloemfontein Vitamin A trial on mother-to-child transmission of HIV was informed and voluntary.

Methods: Private interviews using a structured questionnaire was conducted with Vitamin A trial participants (n=92) attending postnatal follow-up trial visits during a three month period.

Results: Only 3.3% stated that they felt forced into taking part in the trial, but 92.3% stated that they felt they would no longer get good medical care if they withdraw from the trial. Knowledge about the trial was poor.

Conclusion: Great care should be taken to ensure that patients understand the information given to them.

Introduction:

According to international regulatory authorities[1] as well as local institutional guidelines[2] informed consent is a prerequisite for participation in every clinical trial. Consent implies that participation is voluntary. Furthermore, the participant must know the implications of participation[3]. Even if a participant has signed an informed consent form the participant does not necessarily understand what the participation will entail, and consent may thus not be informed[4]. On the other hand, a study conducted in a South African hospital found that patient consent for HIV testing was informed but not truly voluntary[5].

The aim of this study was to investigate whether the consent for HIV testing and subsequent participation in a randomised, double-blind, placebo-controlled trial investigating the effect of Vitamin A on mother-to-child transmission of HIV[6] was informed and voluntary. Participants' knowledge regarding HIV/AIDS and the trial was used to measure how informed their consent was, and participants' perceptions regarding their willingness to participate, ability to withdraw, and whether they would no longer get good medical care if they withdraw were used to measure how voluntary the consent was. The trial was conducted from September 1997 to December 2000 in Bloemfontein, Free State province, South Africa. In 1997 in the annual survey of the South African Department of Health of women attending public health antenatal clinics 20% of Free State women were found to be HIV positive, with the national figure being 17%[7]. Despite these figures there has been no routine intervention aimed at preventing vertical transmission in South Africa.

Methods:

Participants in the Bloemfontein Vitamin A trial were 303 HIV positive women from metropolitan Bloemfontein. The majority (56%) lived in informal settlements, and all attended public health facilities. For the trial women were asked to volunteer for HIV testing during their first antenatal visit. Pre-test counselling was done in groups and post-test counselling individually. Seropositive women were asked to participate in the trial. All trial participants gave separate informed consent for the trial. All patients were recruited by one study physician, and received information verbally and in writing in Sesotho, English or Afrikaans information sheets.

The sample for this descriptive study consisted of all women attending postnatal follow-up trial visits from mid-July 1999 to mid-October 1999. Private interviews using a structured questionnaire in Afrikaans or Sesotho were conducted by a retired nursing matron, fluent in Sesotho, Afrikaans and English. Selected information was taken from the patient's trial case record form.

Results:

Of the 96 patients approached for inclusion in this study, 4.2% refused to participate. Ninety-six percent of interviews were conducted in Sesotho. The median age of the 92 respondents was 27 years. Their median education level was std 8 (10 years schooling), with 87.9% having attended high school (std 6 or higher). The median time since inclusion into the trial was 14 months.

The vast majority indicated that they were counselled and gave consent for HIV testing (Table 1). Knowledge regarding HIV transmission and prevention was generally good with more than 80% giving correct answers regarding modes of transmission.

Only 3.3% stated that they felt obliged to take part in the trial. However, only 24.2% felt that they could withdraw at any time and 92.3% stated that they thought they would no longer get good medical care if they withdraw from the trial (Table 1). Knowledge about the trial was poor (Table 2).

Discussion:

The time which had elapsed between the patient's HIV test and inclusion into the trial, and the interview was on average more than a year, which could influence recall. Furthermore, non-attendance was a problem in the trial[6] and respondents in this study are likely to be the most positive and informed participants, having remained in the trial for so long. Any estimates regarding the extent of the consent being informed and voluntary may therefore be over-estimates.

The good knowledge regarding HIV/AIDS transmission and prevention may reflect the good knowledge which exists in the community, rather than good counselling. However, many repondents still had questions regarding HIV (40%) and many had incorrect knowledge or were uncertain about the fatality and cure of HIV.

The respondents, despite the majority having 8 years of schooling or more, had poor knowledge about the most basic details of the trial. Their participation can thus not be seen as informed. Repeating and discussing these details at each trial visit may address this problem. In approximately a third of recruiting interviews use was made of Sesotho translators, although the vast majority of patients taking part in the consent study chose to be interviewed in Sesotho. The recruiting doctor who also saw the patients at subsequent trial visits was struck by how few questions were asked by the participants, despite ample opportunity given for questions. Researchers should consider eliciting any problems more actively. Sanne, Firnhaber, Jentsch and Ive[8] have suggested that a social worker should be introduced to participants at the start of a trial to witness the consent procedure and to act as a patient advocate during the trial.

Although the respondents felt that their participation in the trial was voluntary, they were clearly aware of the lack of alternative sources of care. During the time of this trial the lack of routine treatment for HIV positive pregnant women in South Africa received wide-spread media attention.

Acknowledgements:

We wish to thank V de W Brandt, CE Henning and JW Henning, three 5th year medical students, who wrote the initial protocol for this project under the supervision of the Vitamin A project team; A Motsalamadi, the interviewer; and the Vitamin A trial participants.

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Table 1: Vitamin A trial participants' perceptions regarding HIV testing and trial participation

	Yes	No	Unsure
HIV testing			
Was counselling given to you before the HIV test (n=92)	94.6%	5.4%	0%
If yes			
Did you understand the counselling (n=86)?	95.3%	3.5%	1.2%
Do you feel you now know enough about HIV(n=86)	41.9%	55.8%	2.3%
Do you have more questions about HIV (n=91)	39.6%	60.4%	
Did you consent to be tested for HIV?	98.9%	1.1%	0%
Trial participation (n=91)			
Did you want to participate in the trial?	98.9%	1.1%	0%
Did you feel forced to take part in the trial?	3.3%	96.7%	0%
Can you withdraw from the trial at any time?	24.2%	73.6%	2.2%
Were you allowed to ask questions when you decided to take part in the trial?	91.2%	8.8%	0%
Do you feel that you will no longer get			

good medical care when you stop taking part in the trial?	92.3%	7.7%	0%

Table 2: Vitamin A trial participants' knowledge regarding the trial (n=92)

Medication used in trial	
Vitamin A (correct answer)	40.2%
vitamins	5.4%
description given of appearance	13.0%
unsure	35.9%
other incorrect answers	5.5%
Reason why medication is administered	
mother-to-child transmission (correct answer)	28.3%
cure HIV	26.1%
unsure	17.4%
doctor did not explain or I did not ask	6.5%
other incorrect answers	21.7%
Till when postnatal visits must continue	
18 months (correct answer)	30.4%
unsure	33.7%
have not been told	9.8%
until doctor says I must stop	9.8%
other incorrect answers	16.3%

APPENDIX 2

Patient information sheet

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Patient Information Sheet

Mother to child transmission of HIV may occur during pregnancy, at delivery or during breast-feeding. The contribution of each of these routes to the overall risk has not been clearly quantified.

Pregnancy and HIV infection are associated with vitamin A deficiency and low maternal vitamin A levels was found to be associated with mother-to-child HIV transmission. This has lead to suggestions that vitamin A administration during pregnancy and after delivery period may help to prevent or reduce mother-to-child HIV transmission. Providing vitamin A to breast-feeding mothers and their infants at the same time may substantially reduce the risk of HIV transmission to infants who have escaped infection during pregnancy or delivery, and may reduce early infant mortality, due to improved immune function. Side-effects that may be experienced by some patients include nausea and headache. However, if a low dose of vitamin A is used, no side effects are expected.

The vitamin A study in which you will participate is a medical research project which will involve 400 patients and it is divided into **two Phases**. Phase I is the pregnancy period and Phase II is after delivery (mother-infant pairs) until the baby is 18 months old. The study will investigate the efficacy of an oral dose of vitamin A compared to placebo, given to pregnant women, subsequent lactating mothers and their infants after delivery to reduce mother-to-child transmission of HIV.

During Phase I of the study you will be expected to take a capsule of the study medication every day and return to the clinic for observation and collection of study medication once every two months for the rest of your pregnancy. At the first visit the doctor will perform a complete physical examination, demographic data will be collected as well as a complete medical history. Blood samples will be taken for investigations. At the 2nd and 3rd visits the doctor will record the relevant medical history and perform a relevant physical examination, blood samples will be taken and another packet of study medication will be given to you.

Phase II of the study will start when your baby will be one month old. You and your baby will be expected to take study medication at every visit. At the first visit (baby will be one month old) the doctor will take a complete medical history and perform a complete physical examination of the baby, update medical history and demographic data, and perform a relevant physical examination on you. Blood samples will be taken from you and your baby for investigations. The study medication will be administered to you and your baby. The same procedure will be followed at each visit. You must return for a follow up visit when your baby is 3, 6 , 9, 12 and 15 months old. When the baby is 18 months old you must return for post treatment assessment. The doctor will collect relevant information and perform relevant physical examinations on you and the baby. At this stage you will have completed your participation in the study.

The information provided by this study will help doctors to know possible ways of preventing or reducing mother-to-child HIV transmission. It will help policy makers and public health specialists to implement affordable health programs for women and children aimed at reducing mother-to-child HIV transmission in developing countries.

Participation in this study is entirely voluntary. You may also withdraw from the study at any point and for any reason. If you should decide to withdraw from the study, you are encouraged to inform your doctor and return to the clinic for one last visit where your doctor can examine you and take some blood samples for investigation to ensure that there has not been any side-effects of the study medication. Your doctor may also withdraw you from the study if he/she considers it necessary. All treatment and investigations related to this study will be paid for by the investigator. You will only have to pay for your own treatment that is not related to the study. In the event of any illness or injury occurring, you should contact your doctor immediately or inform him/her at your next visit to the clinic. Transport costs to and from the clinic at every visit will be provided.

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TLHAHISOLESEDING YA MOKUDI

Phetisetso ya vaerase ya HIV ngwaneng ho tswa ho mmae, e ka etsahala nakong ya boimana, ya ho pepa, kapa nakong ya phepo ya letswele. Seabo sa mokgwa ka mong oo vaerase ya HIV e ka fetiswang ka ona le kotsi ya yona ha e eso ka e hlakiswa hantle.

Boimana le tshwaetso ya vaerase ya HIV di amangwa le kgaello ya vithamine A le bophahamo bo tlase ba vithamine A ya mosadi, ho hlahelletse hore di amana le phetisetso ya vaerase ya HIV ngwaneng ho tswa ho mmae. Sena se tlisitse tshisinyo tse reng phumantso ya vithamine A nakong ya boimana le ka mora nako ya ho pepa e ka thusa ho thibela kapa ho fokotsa phetisetso ya vaerase ya HIV ngwaneng ho tswa ho mmae. Kabelo ya vithamine A basading ba nyantshang le maseeng a bona ka nako e le nngwe, e ka fokotsa kotsi ya phetisetso ya HIV maseeng a phonyohileng tshwaetso nakong ya boimana kapa nakong ya ho pepa, mme kabelo ya vithamine A e ka ntlafatsa tshebetso ya tshireletseho kgahlano le mafu, mme sena se thibele ho hlokahala ha masea. Ditlamorao tse mpetse ka nnang a fumanwa ke bakudi ba bang di kenyelletsa ho feroha dibete (nausea) le ho opa ha hloho. Le ha ho le jwalo, haeba ho sebedisitswe tekanyetso e nyenyane ya vithamine A ha ho a lebellwa ditlamorao tse mpe.

Thuto tse mabapi le vithamine A tseo o tla bang le seabo ho tsona, ke tse mabapi le projeke ya dipatlisiso tsa bongaka e kenyelletsang bakodi ba 400 mme e arotswe ha bedi. Kaorlo ya 1 ke nako ya boimana mme karolo ya 2 ke ka mora ho pepa (karolo ya batswetse le masea) ho fihlela lesea le se le le dikgwedi tse 18. Thuto ena e tla fuputsa ka ditlamorao tsa ditekanyetso (dose) tsa vithamine A, papisong le placebo, e fuwang basadi ba immeng ba

nang le vaerase ya HIV, le ho fuwa basadi ba nyantshang le masea a bona kamora ho pepa ho ka fokotsa phetisetso ya vaerase ya HIV ngwaneng ho tswa ho mmae.

Nakong ya Karolo ya 1 ya thuto ena, ho tla lebellwa howena hore o nwe pilisi (capsule) merianeng ya dithuto tsena letsatsi ka leng mme o tle o kgutlele tleliniking bakeng sa hlahlobo le ho nka meriana hanngwe kgweding tse pedi nakong yohle ya boimana. Ketelong ya pele Ngakeng , Ngaka e tla phetha hlahlobo e phethahetseng ya mmele, ho bokellwe tlhahisoleseding ya dipalopalo tsa ba tswalwang ha mmoho le boitshetleho ka boemo ba bophelo ho fihlela nakong ena. Mehlala ya madi e tla nkuwa bakeng sa diphuputso. Ketelong ya bobedi le ya boraro ngakeng, ngaka e tla ngola faatshe pale ya bongaka mme a etse hlahlobo e hlokehang ya mmele, madi a tla nkwa mme o tla fuwa hape pakana e nngwe ya moriana bakeng sa thuto.

Karolo ya bobedi ya thuto e tla qala ha ngwana wa hao a se a le kgwedi e le nngwe. Wena le lesea la hao le tla lebellwa hore le nke meriana ya thuto ketelong e nngwe le e nngwe. Ketelong ya pele (lesea ha le le kgwedi) ngaka e tla nka pale ya bongaka e feletseng ho tswa ho ngwana mme a mo hlahlobe ka ho felella, o tla lokisa le ho beha ka toka dipalopalo mme ka mora moo a hlahlobe wena. Mehlala ya madi e tla nkwa ho tswa ho wena le lesea la hao bakeng sa diphuputso. Wena le lesea la ha o le tla fuwa/nweswa meriana ya thuto. Mokgwa ona o tla latelwa ketelong e nngwe le e nngwe. O lokela ho kgutla bakeng sa hlahlobo botjha ha lesea le se le le dikgwedi tse 3, 6, 9, 12 le 15. Ha lesea le le dikgwedi tse 18 o lokela ho kgutla bakeng sa ho tla lekola ditlamorao tsa phekolo. Ngaka e tla bokeletsa tlhahisoleseding e hlokehang mme a etse ddihlahlobo tsa

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Pasient inligtingsstuk

Moeder na kind transmissie van HIV kan gedurende swangerskap, tydens kraam, of tydens borsvoeding plaasvind. Die bydrae van die elk van hierdie roetes tot die algehele risiko is nog nie presies gedefinieer nie.

Swangerskap en HIV infeksie is geassosieer met vitamien A gebrek, en lae vlakke van vit A in swanger vrouens is gevind om geassosieer te wees met moeder to kind oordrag van HIV. Dit het aanleiding gegee tot spekulasie dat die toediening van vit A tydens swangerskap kan lei tot 'n afname in moeder na kind oordrag van HIV. Verder kan die toediening van vit A aan lakterende moeders en hulle babas die risiko van oordrag via borsvoeding aan babas, wat infeksie tydens swangerskap en kraam misgeloop het, aansienlik verminder. Vroee mortaliteit tydens babajare kan ook verminder word a.g.v. verbeterde immuunfunksie. Newe-effekte wat deur sommige pasiente ondervind kan word is hoofpyn en naarheid, maar met 'n lae dosis van vit A word geen newe-effekte verwag nie.

Die vit A studie waaraan u deelneem is 'n mediese navorsingsprojek wat 400 pasiente sal betrek en ingedeel is in 2 fases. Fase I is die swangerskaps periode en fase II (moeder/kind pare) volg na kraam en duur totdat die baba 18 maande oud is. Die studie sal ondersoek instel na die effektiwiteit van orale dosisse van vit A teenoor plasebo, wat toegedien word aan swanger en lakterende vroue asook hulle babas, om moeder na kind transmissie van HIV te voorkom.

Gedurende fase I sal van u verwag word om elke dag 'n kapsule van die studie medikasie te neem en om terug te keer na die kliniek vir observasie en die verkryging van medikasie elke twee maande vir die res van u swangerskap. Tydens die eerste besoek sal die geneesheer 'n geskiedenis neem, 'n volledige fisiese ondersoek doen, en u demografiese data sal afgeneem word. Bloedmonsters sal geneem word vir laboratorium ondersoeke. Tydens die 2de en 3de besoeke sal die dokter die relevante mediese geskiedenis neem en 'n fisiese ondersoek uitvoer. Bloedmonsters sal ook geneem word en 'n verdere pakkie studie medikasie aan u verskaf word.

Fase II van die studie sal begin as u baba 1 maand oud is. Van beide u en u baba sal verwag word om medikasie te neem by elke besoek. Tydens die eerste besoek (baba 1 maand oud) sal die geneesheer 'n volledige geskiedenis en ondersoek van die baba doen, asook 'n relevante fisiese ondersoek op u. Geskiedenis en demografiese data sal ook opgedateer word. Bloedmonsters sal van u en die baba geneem word vir laboratorium ondersoeke. Die studie medikasie sal aan u en die baba toegedien word. Dieselfde prosedure sal by elke besoek gevolg word. U moet terugkom vir opvolgbesoeke wanneer u baba 3, 6, 9, 12 en 15 maande oud is. Wanneer die baba 18 maande oud is moet u terugkom vir post-behandelinsevaluasie. Die geneesheer sal dan relevante inligting versamel en relevante kliniese ondersoeke op u en u baba doen. Op hierdie stadium is u deelname aan die studie voltooi.

Die inligting wat deur hierdie studie gelewer sal word sal help om geneeshere bewus te maak moontlike metodes vir die voorkoming of vermindering van moeder tot kind oordrag van HIV. Dit sal ook bydra om beleidsmakers en gemeenskapsgesondheids spesialiste te help om bekostigbare gesondheids programme, wat daarop gemik is om moeder tot kind transmissie van HIV te verminder, vir moeders en kinders in ontwikkelende lande te implementeer.

Deelname aan die studie is geheel en al vrywillig. U kan ook van die studie onttrek op enige stadium en vir enige rede. Indien u sou besluit om te onttrek van die studie word u aangemoedig om terug te keer na die kliniek vir 'n laaste besoek waar die dokter u sal ondersoek en bloedmonsters sal neem vir ondersoek om enige moontlike newe-effekte van die studie medikasie uit te skakel. U dokter mag u ook van die studie onttrek indien hy/sy dit nodig vind.Alle behandeling en ondersoeke geassosieer met die studie sal deur die ondersoeker betaal word. U sal net hoef te betaal vir u eie behandeling wat nie met die studie verband hou nie. In geval van siekte moet u met u dokter in verbinding tree of hom/haar inlig by u volgende kliniekbesoek. Vervoer na en van die kliniek sal vergoed word.

APPENDIX 3

Consent form for HIV test

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Mrs P Chikobvu
Phone (051) 4013189

VITAMIN A STUDY

CONSENT FORM FOR HIV TEST

I, Ms_____ have given permission to have my blood taken and tested for HIV. I certify that I have been properly counselled

Signature Patient_____ Date _____
dd mm yy

Signature Counsellor_____Date _____
dd mm yy

Signature Witness _____ Date _____
dd mm yy

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VITAMIN A STUDY

FOROMO YA TUMELLO YA TEKO YA HIV

Nna, Mof._____Ke fane ka tumello ya ho nkwa ha madi a ka mme a hlahlojwe bakeng sa HIV. Ke netefatsa hore ke ile ka fumana khanseling ka botlalo.

Tshaeno ya Mokudi _____ Mohla

Letsatsi kgwedi selemo

Tshaeno ya Khanselara_____ Mohla

Letsatsi kgwedi selemo

Tshaeno ya Paki _____Mohla

Letsatsi kgwedi selemo

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VITAMIN A STUDY

TOESTEMMINGSVORM VIR HIV TOETS

Ek, me ..... het toestemming gegee dat my bloed getrek kan word en getoets word vir HIV. Ek bevestig dat ek beraad is i.v.m. die implikasies van so 'n toets.

Pasiënt ..... Datum .....

Berader ..... Datum .....

Getuie ..... Datum .....

APPENDIX 4

Consent form for study participation

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Informed consent Form

Name:_____

Date of birth _____/_____/_____/

Address:_____
_____
_____
_____

INFORMED CONSENT TO PARTICIPATE IN A DOUBLE-BLIND RANDOMISED CONTROLLED TRIAL TO ASSESS THE EFFICACY OF ORAL DOSE OF VITAMIN A COMPARED TO PLACEBO IN HIV SEROPOSITIVE PREGNANT WOMEN, SUBSEQUENT LACTATING MOTHERS AND THEIR INFANTS ON VERTICAL (MOTHER-TO-CHILD) TRANSMISSION OF THE VIRUS.

I, _____, have been adequately informed concerning the basis of the study protocol by Dr._____, and understand fully the purpose, conditions and duration of the VITAMIN A study and the resultant demands on me (e.g taking medication regularly). I have received a summary of this information in writing.

I am prepared to take part in the Vitamin A study and to take the medication for the rest of my pregnancy. I am prepared to continue taking the medication after delivery. I am also prepared to enrol my coming baby in the study, which means that the baby will be given Vitamin A or placebo every 3 months from one month of age. I understand that neither I nor the supervising doctor will know which medication I am taking, Vitamin A containing or not. I will follow the medical instructions given for carrying out the study, but reserve the right to withdraw at any time and for any reason. Withdrawal will not cause any disadvantage to me. If necessary, the supervising doctor

may withdraw me from the study. If questions arise concerning the study itself and my rights as a participant in it, I can contact Dr._____ at any time.

I will be notified of any significant new findings regarding the use of vitamin A. I agree that any information about me connected with this study will be handled confidentially and can be stored and evaluated or passed on for scientific purposes, but that my name will be kept confidential. Only health authorities, commissioners and representatives of the principal investigator are allowed to inspect the records.

_____ d d m m y y
Signature of Physician |__|__|__|__|__|__| *Date*

_____ d d m m y y
Signature of Participant |__|__|__|__|__|__| *Date*

_____ d d m m y y
Signature of Witness |__|__|__|__|__|__| *Date*

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Foromo ya tumello

Lebitso:_____

Letsatsi la tswalo _____/_____/_____/

Aterese:_____
_____
_____
_____

TUMELLO YA HO NKA SEABO TEKONG E LAOLWANG KA HO SE QOLLE E LE HO LEKOLA DITLAMORAO TSE LEBELETSWENG TSA VITHAMINE A, E NOWANG HA HO BAPISWA LE PLACEBO BAIMANENG BA NANG LE VAERASE YA HIV, BOMMENG BA NYANTSHANG LE MASEYENG A BONA, KA PHETISETSO E TSEPAMENG YA VAERASE(MME HO NGWANA)

Nna,_____, ke fuwe tlhahisoleseding ka botlalo mabapi le motheo wa dithuto tsena ke Ngaka_____,ke utlwisisa ka hohle sepheo, maemo le nako ya dithuto tsa Vithamine A le hore ho lebeletsweng ho tswa ho nna (mohlala, ho nwa meriana ka tshwanelo). Ke fumane kgutsufatso ya tlhahisoleseding ena ka mokgwa wa lengolo.

Ke ikemiseditse ho nka karolo dithutong tsa Vithamine A le ho nka meriana nakong yohle ya boimana ba ka. Ke ikemiseditse ho tswella ka meriana le ka mora hoba ke pepe. Ke ikemiseditse hape le ho ngodisa lesea la ka dithutong, ka mantswe a mang lesea le tla fumantshwa Vithamine A, kapa placebo dikgwedi tse ding le tse ding tse tharo ho tloha kgweding ya pele ya tswalo. Ke utlwisisa hore nna kapa ngaka e ntlhahlobang ha re na ho tseba mofuta wa moriana oo ke o sebedisang, hore o na le Vithamine A kapa tjhee. Ke tla latela ditaelo tsa bongaka tsa dithuto tsena, empa ke boloke tokelo ya ka ya ho ikgula neng kapa neng ka lebaka lefe kapa lefe. Ho ikgula ha ka ho ka se ntshenyeletse ditaba. Ha ho hlokeha, ngaka e hlahlobang e ka mpehella thoko dithutong. Ha dipotso di hlaha mabapi le dithuto ka botsona le ditokelo tsa ka jwaleka motho ya nkang karolo ho tsona, ke tla buisana le

Ngaka_____ka nako tsohle

Ke tla tsebiswa ka ditlamorao tse ikgethileng mabapi le tshebediso ya Vithamine A. Ke a dumela hore tlhahisoleseding efe kapa efe ka nna e amanang le dithuto tsena e tla ba patuwe, mme e tla bolokwa le ho lekolwa kapa e fetisetswe pele bakeng sa

ditshebetso tsa mahlale, empa lebitso la ka le tla dula le patehile. Ke feela baokamedi ba bophelo bo botle, bakomishenara, le baemedi ba mofuputsi ya ka sehloohong ba dumeletsweng ho ka sheba direkoto.

_____ /_____/_____/_____/

Tshaeno ya Ngaka letsatsi / kgwedi / selemo

_____ /_____/_____/_____/

Tshaeno ya Motho ya nkang karolo letsatsi / kgwedi / selemo

_____ /_____/_____/_____/

Tshaeno ya Paki letsatsi / kgwedi / selemo

DIE UNIVERSITEIT VAN DIE ORANJE-VRYSTAAT

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Fakulteit Geneeskunde

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Ingeligte Toestemming Vorm

_____

Naam:_____

Geboortedatum:____/____/____

Adres: _____

_____

_____

_____

INGELIGTE TOESTEMMING OM DEEL TE NEEM, AAN 'n GEKONTROLEERDE DUBBELBLINDE GERANDOMISEERDE STUDIE OM DIE EFFEK VAN ORALE DOSISSE VAN VITAMIEN A IN VERGELYKING MET PLASEBO, IN HIV POSITIEWE SWANGER/LAKTERENDE VROUE EN HULLE BABAS, OP DIE VERTIKALE (MOEDER/KIND) TRANSMISSIE VAN DIE VIRUS.

Ek, _____, is toereikend ingelig i.v.m. die studie protokol deur Dr. _____ en verstaan in geheel die doel, omstandighede en duur van die VITAMIEN A studie, sowel as die gevolglike verpligtinge op my (bv. gereelde neem van medikasie). Ek het 'n skriftelike opsomming van die inligting ontvang.

Ek is bereid om deel te neem aan die VITAMIEN A studie en om die medikasie te neem vir die res van my swangerskap. Ek is ook bereid om my komende baba aan die studie te laat deelneem, wat beteken dat die baba vitamien A, of plasebo elke 3 maande vanaf 1 maand ouderdom sal ontvang. Ek verstaan dat nie ek, of die studie monitor, sal weet watter medisyne ek neem nie, vitamien A bevattend of nie. Ek sal die mediese instruksies vir die uitvoer van die studie nakom, maar behou die reg om ten enige tyd, en vir enige rede, aan die studie te onttrek. Onttrekking sal my nie benadeel op enige wyse nie. Indien nodig mag die moniterende dokter my van die studie onttrek. Indien vrae oor die studie of my deelname daaraan ontstaan kan ek Dr._____ kontak te eniger tyd.

Ek sal ingelig word aangaande enige nuwe bevindinge rakende vitamien A. Ek kom ooreen dat enige inligting rakende my in verband met die studie konfidensieel hanteer sal word, dat dit gestoor kan word en oorgedra kan word vir wetenskaplike doeleindes, maar dat my naam vertroulik sal bly. Slegs gesondheidsowerhede, en verteenwoordigers van die hoofnavorser sal toegelaat word om die rekords te inspekteer.

_____ ____/____/_____

Dokter se handtekening *Datum*

_____ ____/____/_____

Deelnemer se handtekening *Datum*

_____ ____/____/_____

Getuie se handtekening *Datum*

APPENDIX 5

Case Record Form (CRF)

Instructions

PHASE ONE: PRE-DELIVERY

Visit 1

Visit 2

Visit 3 (not included, pages are identical to visit 2)

Any visit: Other medication

PHASE TWO: MOTHER-INFANT PAIRS

Post-delivery 1 month (Visit 1)

Post-delivery 3 months

Post-delivery 6 months (not included pages are identical to post-delivery 3 months)

Post-delivery 9 months

Post-delivery 12 months (not included pages are identical to post-delivery 3 months)

Post-delivery 15 months (not included pages are identical to post-delivery 9 months)

Post-delivery 18 months (not included pages are identical to post-delivery 3 months)

Any visit: Adverse events

Premature termination

Any visit: Other medication

Study termination form

Study medication record

PATIENT'S INITIALS	PATIENT NUMBER	HOSPITAL NUMBER

A double-blind, randomised, controlled trial to assess the efficacy of an oral dose of vitamin A compared to placebo, in HIV pregnant women, subsequent lactating or non-lactating mothers and their infants on vertical HIV transmission

PATIENT'S INITIALS	PATIENT NUMBER	HOSPITAL NUMBER

INSTRUCTIONS FOR COMPLETING THE CASE REPORT FORM

Please read carefully

1. Use black ballpoint pen and print all entries legibly.
2. Complete the header information on each CRF page, using the appropriate Patient Initials, Patient Number and Hospital Number.
3. Enter the patient's initials in the order of first initial, second initial, third initial and surname. Enter (-) for missing initials.
4. Complete all items. A blank or no entry will require follow-up which can be time consuming. If, for some reason, an item of information is unavailable or a test is not performed, please record 'ND' (not done) in the appropriate place on the CRF, rather than leaving it blank. If however, the data is unknown please enter 'u'.
5. Enter '0' (zero) rather than a period, slash or dash for any questions requiring an answer of zero.
6. Do not use correction fluid or try to erase if a mistake occurs. Instead, draw a single line through the error, record the correct information, and then initial and date the change outside the data areas.
7. Where appropriate, indicate choices, for example, yes/no, male/female, by marking the relevant box with a tick '✓'.
8. When there is a choice of scores defined in the CRF, please record a number (for example: 1 = mild, 2 = moderate, 3 = severe). Do not record combinations of numbers (for example: '1-2', '1/2' etc.). More than one discrete number may be recorded, if indicated (for example: Action taken on the Adverse Events Record).
9. Restrict the writing or marking to the appropriate areas so that the mark does not extend into other data or shaded areas.
10. Avoid abbreviations which data processing personnel may not understand.
11. Make comments only in spaces provided and be concise.
12. Record all dates in the form dd/mm/yy (day/month/year), using a total of six digits. For example, if the date of the examination is 4th July 1996 then record '04/07/96' on the form. Record all times in 24-hour clock, i.e. 2:00 pm would be recorded as '14:00' hours, midnight as 00:00 and midday as 12:00 hours.
13. Every effort should be made to obtain complete dates. If a patient cannot remember a specific day or month, the closest approximation should be obtained within at least a year. Complete dates for Adverse Events and Study medication dose changes however, are crucial.

SCHEDULE OF OBSERVATIONS

Clinic visit		1	2	3	Premature Termination
Trimester	**1**	X	X	X	-
	2	X	X		
	3	X			
Informed consent		X	-	-	-
Inclusion/Exclusion criteria		X	-	-	-
Randomisation		X	-	-	-
Demographic data		X	-	-	-
Medical history		X	X	X	-
Vital signs and Physical examination		X	X	X	X
Laboratory evaluation		X	-	-	X
Medication accountancy		X	X	X	X
Adverse events		-	X	X	X

Note: If during pregnancy, woman terminates participation prematurely, please fill in premature termination form (mother) on Pages 63 and 64.

Visit 1

INSTRUCTIONS

Please read the instructions carefully

1. Please record and complete the following at enrollment:
   - Date of visit
   - Obtain written Informed Consent
   - Inclusion/Exclusion criteria
   - Demographic data
   - Vital signs and Physical examination
   - Medical history
2. Please take blood samples for laboratory measurements.
3. Administer the first capsule to the patient and give the appropriate packet of medication to the patient. Advise her to take one capsule per day orally with some tap water and then mark the date and approximate time the capsule was taken on the diary provided.
4. Document receipt of the capsule by the woman.
5. Make an appointment for the next visit within a period of 2 months and ask the patient to return all unused capsules at the next visit.

PATIENT'S INITIALS	PATIENT NUMBER	HOSPITAL NUMBER

Visit 1

INCLUSION CRITERIA

Investigator's initials: _____

Please answer all questions

		No	Yes
1.	Is the woman attending either Pelonomi, Universitas or MUCPP ante-natal clinics ?	☐ 1	☐ 2
2.	Is the patient willing to participate in the study ?	☐ 1	☐ 2
3.	Does the patient have the ability to comprehend and is she willing to sign the statements of the informed consent ?	☐ 1	☐ 2
4.	Is the woman HIV positve ?	☐ 1	☐ 2
5.	Is the patient prepared or able to come for regular follow-up ?	☐ 1	☐ 2

*If any of the answers is **NO**, please **exclude** the patient*

Visit 1 | **EXCLUSION CRITERIA** | **Investigator's initials:** _____

Please answer all questions

		No	Yes
1.	Is the patient's pregnancy more than 36 weeks ?	☐ 1	☐ 2
2.	Does the patient have evidence of psychiatric disorder, antagonistic personality, poor motivation, emotional or intellectual problems likely to limit the validity of consent to participate in the study, or limit the ability to comply with protocol requirements ?	☐ 1	☐ 2
3.	Did the patient participate in another study with an experimental drug within 8 weeks of commencement of the clinical phase of this study ?	☐ 1	☐ 2

*If any of the answers is **YES**, please **exclude** the patient*

Investigator's signature_____ **Date** |_|_|_|_|_|_| d d m m y y

Visit 1 | **DEMOGRAPHIC DATA** | **Investigator's initials:** _____

Date of visit : ☐☐☐☐☐☐ (d d m m y y)

Date of birth ☐☐☐☐☐☐ **or** (d d m m y y)

Age ☐☐ years

Height ☐☐☐ cm

Body mass ☐☐☐ • ☐ kg

Race
- ☐1 White
- ☐2 Black
- ☐3 Coloured
- ☐ Other, specify : _____

Home language
- ☐1 Afrikaans
- ☐2 English
- ☐3 Sotho, Tswana,
- ☐4 Tswana
- ☐5 Xhosa
- ☐ Other, specify : _____

Home address : _____

_____

_____

Telephone : _____

Next of kin (Name) : _____

Relationship : _____

Address : _____

_____

Telephone : _____

Visit 1 | **PREVIOUS MEDICAL CONDITIONS** | **Investigator's initials:** _____

Are there any operations, allergies or illnesses, (excluding study indication) prior to or on entry to the trial ?

No ☐ 1
Yes ☐ 2 **, please specify below**

Relevant past or current findings *(as determined by the investigator)* *List only ONE disease or finding per line*	**Onset date** ***or date of diagnosis*** ***(Enter at least year)*** ***(ddmmyy)***
1.	
2.	
3.	
4.	
5.	
6.	
7.	
8.	
9.	
10.	

* If worsened please enter details on the Adverse Events page (Page 59).

Visit 1 | **MEDICAL HISTORY** | **Investigator's initials:** _____

Date: ☐☐ ☐☐ ☐☐ (d d m m y y)

History of	No	Yes	If Yes, please comment
General			
Night sweats	☐1	☐2	
Fever	☐1	☐2	
Cough	☐1	☐2	
Nausea / Vomiting	☐1	☐2	
Neurologic			
Headaches	☐1	☐2	
Confusion	☐1	☐2	
Obstetrical			
Stage of pregnancy	☐1 1st trimester: ☐☐ weeks		
	☐2 2nd trimester: ☐☐ weeks		
	☐3 3rd trimester: ☐☐ weeks		
Others, specify : _____			

Parity: ☐☐ veries

Gravity: ☐4 pregnancies

Expected date of delivery: ☐☐ ☐☐ ☐☐ (d d m m y y)

Please complete the Other Medication form on Page 18.

Visit 1

VITAL SIGNS AND PHYSICAL EXAMINATION

Investigator's initials: _____

Measurement	Value :
Systolic BP (mmHg)	☐☐☐
Diastolic BP (mmHg)	☐☐☐
Heart rate (beats/min)	☐☐☐
Heart sounds : _____	
Other, specify : _____	

	Normal	Abnormal*	Not done
General (anemia jaundice)	☐1	☐2	☐3
Skin	☐1	☐2	☐3
ENT	☐1	☐2	☐3
LN	☐1	☐2	☐3
Respiratory examination	☐1	☐2	☐3
CVS examination	☐1	☐2	☐3
GIT examination	☐1	☐2	☐3
UG tract examination	☐1	☐2	☐3
CNS examination	☐1	☐2	☐3
Other abnormalities, specify:	☐1	☐2	☐3
_____	☐1	☐2	☐3
_____	☐1	☐2	☐3

* If abnormal, please complete the Adverse event page (Page 59).

COMPUTER NUMBER

Visit 1

LABORATORY DATA

Investigator's initials: _____

Haematology No. _____	**Result***
Haemoglobin	
Haematocrit	
RBC - Erythrocytes	
Thrombocytes	
Total WBC - Leukocytes	
Lymphocytes	
Neutrophils	
Monocytes	
Eosinophils	
Basophils	
Other : _____	

Virology No. _____	**Result**
RPR	
CD4 counts	
CD8 counts	
CD4/CD8 ratio	
Plasma viral load	

* If the result is a clinically significant abnormality, please complete the Adverse Events page

Visit 2

INSTRUCTIONS

Please read the instructions carefully

1. Please record and complete the following:
   - Date of visit
   - Vital signs and Physical examination
2. Administer the first capsule to the patient and give the appropriate packet of medication to the patient. Advise her to take one capsule per day orally with some tap water and then mark the date and approximate time the capsule was taken on the diary provided.
3. Document receipt of the capsule by the woman.
4. Make an appointment for the next visit within a period of 2 months and ask the patient to return all unused capsules at the next visit.

PATIENT'S INITIALS	PATIENT NUMBER	HOSPITAL NUMBER
☐☐☐☐	☐☐☐	☐☐☐☐☐☐☐☐☐☐☐☐

Visit 2

MEDICAL HISTORY

Investigator's initials: _____

Date: ☐☐/☐☐/☐☐☐☐ (d d m m y y)

History of (since the previous visit)	No	Yes	If Yes, please comment
General			
Night sweats	☐1	☐2	
Fever	☐1	☐2	
Cough	☐1	☐2	
Nausea / Vomiting	☐1	☐2	
Neurologic			
Headaches	☐1	☐2	
Confusion	☐1	☐2	
Obstetrical			
Stage of pregnancy	☐1 1st trimester: ☐☐ weeks		
	☐2 2nd trimester: ☐☐ weeks		
	☐3 3rd trimester: ☐☐ weeks		
Others, specify : _____			

Please complete the Other Medication form on page 18.

Visit 2

VITAL SIGNS AND PHYSICAL EXAMINATION

Investigator's initials: _____

Measurement	Value :
Systolic BP (mmHg)	☐☐☐
Diastolic BP (mmHg)	☐☐☐
Heart rate (beats/min)	☐☐☐
Heart sounds : _____	
Other, specify : _____	

	Normal	Abnormal*	Not done
General (anemia jaundice)	☐1	☐2	☐3
Skin	☐1	☐2	☐3
ENT	☐1	☐2	☐3
LN	☐1	☐2	☐3
Respiratory examination	☐1	☐2	☐3
CVS examination	☐1	☐2	☐3
GIT examination	☐1	☐2	☐3
UG tract examination	☐1	☐2	☐3
CNS examination	☐1	☐2	☐3
Other abnormalities, specify:	☐1	☐2	☐3
_____	☐1	☐2	☐3
_____	☐1	☐2	☐3

* If abnormal, please complete the Adverse event page (Page 59).

PATIENT'S INITIALS	PATIENT NUMBER	HOSPITAL NUMBER

Any visit: Pre-delivery

OTHER MEDICATION

Investigator's initials: _____

Other medication ? ☐ 1 **No** ☐ 2 **Yes**

If yes, give details:

Description	Trade Name	Daily dose administered	Date started (dd/mm/yy)	Date stopped (dd/mm/yy)

PHASE TWO

MOTHER - INFANT PAIRS

PATIENT'S INITIALS	PATIENT NUMBER	HOSPITAL NUMBER

SCHEDULE OF OBSERVATIONS

Clinic visit	1	2	3	4	5	6	7	Premature Termination
Age of baby in months	1	3	6	9	12	15	18	-
Demographic data (if necessary)	X	-	-	-	-	-	-	-
Medical History	X	X	X	X	X	X	X	-
Vital signs and Physical examination	X	X	X	X	X	X	X	X
Laboratory evaluation	X	X	X	-	X	-	X	X
Adverse events	-	X	X	X	X	X	X	X
End of study	-	-	-	-	-	-	X	X

Note: If mother/infant pairs terminate participation prematurely, please fill in premature termination forms (mother/infant) on Pages 63, 64, 65 and 66.

PATIENT'S INITIALS	PATIENT NUMBER	HOSPITAL NUMBER

Visit 1: Mother and Infant

INSTRUCTIONS

Please read the instructions carefully

1. Please record and complete the following:
   - Date of visit
   - Vital signs and Physical examination
2. Please take blood samples for laboratory measurements for mother and infant.
3. Administer the study medication to the mother and infant.
4. Make an appointment for the next visit when the baby is 3 months old.

PATIENT'S INITIALS	PATIENT NUMBER	HOSPITAL NUMBER

Post-delivery 1 month: Mother

MEDICAL HISTORY

Investigator's initials: _____

Date d d m m y y

History of (since previous visit)	No	Yes	If yes, please comment
General			
Night sweats	☐1	☐2	
Fever	☐1	☐2	
Cough	☐1	☐2	
Nausea / Vomiting	☐1	☐2	
Neurologic			
Headaches	☐1	☐2	
Confusion	☐1	☐2	

Date of delivery : d d m m y y Weight : ___ • ___ kg

Mode of delivery : ☐1 Vaginal ☐2 Caesarean section ☐3 Instrumental assisted

Episistomy : ☐1 No ☐2 Yes Other : _____

If there are any other complications, please complete the Adverse Events page (page 59).

Post-delivery 1 month: Mother | **VITAL SIGNS AND PHYSICAL EXAMINATION** | **Investigator's initials:** _____

Measurement	Value :
Systolic BP (mmHg)	☐☐☐
Diastolic BP (mmHg)	☐☐☐
Heart rate (beats/min)	☐☐☐
Heart sounds : _____	
Other, specify : _____	

	Normal	Abnormal*	Not done
General (anemia jaundice)	☐1	☐2	☐3
Skin	☐1	☐2	☐3
ENT	☐1	☐2	☐3
LN	☐1	☐2	☐3
Respiratory examination	☐1	☐2	☐3
CVS examination	☐1	☐2	☐3
GIT examination	☐1	☐2	☐3
UG tract examination	☐1	☐2	☐3
CNS examination	☐1	☐2	☐3
Other abnormalities, specify:	☐1	☐2	☐3
_____	☐1	☐2	☐3
_____	☐1	☐2	☐3

* If abnormal, please complete the Adverse event page (Page 59).

COMPUTER NUMBER

Post-delivery 1 month: Mother	**LABORATORY DATA**	**Investigator's initials: _____**

Haematology No. _____	**Result***
Haemoglobin	
Haematocrit	
RBC - Erythrocytes	
Thrombocytes	
Total WBC - Leukocytes	
Lymphocytes	
Neutrophils	
Monocytes	
Eosinophils	
Basophils	
Other : _____	

Virology No. _____	**Result**
RPR	
CD4 counts	
CD8 counts	
CD4/CD8 ratio	
Plasma viral load	
Milk viral load	

* If the result is a clinically significant abnormality, please complete the Adverse Events page

PATIENT'S INITIALS	PATIENT NUMBER	HOSPITAL NUMBER

Post-delivery 1 month: Infant

DEMOGRAPHIC DATA

Investigator's initials: _____

Date of birth ☐☐ ☐☐ ☐☐ (d d m m y y)

Sex ☐1 Male ☐2 Female

Length ☐☐☐ cm

Body mass ☐☐ • ☐☐ kg

Head circumference ☐☐ cm

Condition of baby ☐1 Term ☐2 Prem

Type of feeding ☐1 Breast ☐2 Not breast ☐3 Both

Any abnormalities, please specify : _____ _____

_____

_____

Post-delivery 1 month: Infant | **MEDICAL HISTORY / PHYSICAL EXAMINATION** | **Investigator's initials: _____**

Please administer the study medication to the patient. ☐1 **Given** ☐2 **Not given**

History of (since previous visit)	No	Yes	If Yes, please comment
Night sweats	☐1	☐2	
Fever	☐1	☐2	
Cough	☐1	☐2	
Nausea/Vomiting	☐1	☐2	

Feeding: ☐1 Breast ☐2 Not breast. When was breast feeding stopped? |_|_|_|_|_|_| (give at least a month)
d d m m y y

	Normal	Abnormal*	Not done
General appearance	☐1	☐2	☐3
Skin	☐1	☐2	☐3
Eyes	☐1	☐2	☐3
Musculoskeletal	☐1	☐2	☐3
ENT	☐1	☐2	☐3

Heart rate : |_|_|_| beats/min

Blood sample taken ? ☐1 No ☐2 Yes

* If abnormal, please complete the Adverse event page (Page 61).

COMPUTER NUMBER

Post-delivery 1 month: Infant | **LABORATORY DATA** | **Investigator's initials: _____**

Haematology No. _____	**Result***
Haemoglobin	
Haematocrit	
RBC - Erythrocytes	
Thrombocytes	
Total WBC - Leukocytes	
Lymphocytes	
Neutrophils	
Monocytes	
Eosinophils	
Basophils	
Other : _____	

Virology No. _____	**Result**
RPR	
CD4 counts	
CD8 counts	
CD4/CD8 ratio	
Plasma viral load	
ELISA/WB	
PCR	

* If the result is a clinically significant abnormality, please complete the Adverse Events page

PATIENT'S INITIALS	PATIENT NUMBER	HOSPITAL NUMBER

Post-delivery 3 months: Mother and Infant

INSTRUCTIONS

Please read the instructions carefully

1. Please record and complete the following:
   - Date of visit
   - Vital signs and Physical examination
2. Please take blood samples for laboratory measurements for mother and infant.
3. Administer the study medication to the mother and infant.
4. Make an appointment for the next visit when the baby is 6 months old.

PATIENT'S INITIALS	PATIENT NUMBER	HOSPITAL NUMBER

Post-delivery 3 months: Mother

MEDICAL HISTORY

Investigator's initials: _____

Date d d m m y y

History of (since previous visit)	No	Yes	If yes, please comment
General			
Night sweats	☐1	☐2	
Fever	☐1	☐2	
Cough	☐1	☐2	
Nausea / Vomiting	☐1	☐2	
Neurologic			
Headaches	☐1	☐2	
Confusion	☐1	☐2	

Post-delivery 3 months: Mother | **VITAL SIGNS AND PHYSICAL EXAMINATION** | **Investigator's initials:** _____

Measurement	Value :
Systolic BP (mmHg)	___
Diastolic BP (mmHg)	___
Heart rate (beats/min)	___
Heart sounds : _____	
Other, specify : _____	

Please administer the study medication to the patient

☐1 **Given** ☐2 **Not given**

Weight : ___ • ___ **kg**

	Normal	Abnormal*	Not done
General (anemia jaundice)	☐1	☐2	☐3
Skin	☐1	☐2	☐3
ENT	☐1	☐2	☐3
LN	☐1	☐2	☐3
Respiratory examination	☐1	☐2	☐3
CVS examination	☐1	☐2	☐3
GIT examination	☐1	☐2	☐3
UG tract examination	☐1	☐2	☐3
CNS examination	☐1	☐2	☐3
Other abnormalities, specify:	☐1	☐2	☐3
_____	☐1	☐2	☐3
_____	☐1	☐2	☐3

* If abnormal, please complete the Adverse event page (Page 59).

COMPUTER NUMBER

Post-delivery 3 months: Mother | **LABORATORY DATA** | **Investigator's initials: _____**

Haematology No. _____	**Result***
Haemoglobin	
Haematocrit	
RBC - Erythrocytes	
Thrombocytes	
Total WBC - Leukocytes	
Lymphocytes	
Neutrophils	
Monocytes	
Eosinophils	
Basophils	
Other : _____	

Virology No. _____	**Result**
RPR	
CD4 counts	
CD8 counts	
CD4/CD8 ratio	
Plasma viral load	
Milk viral load	

* If the result is a clinically significant abnormality, please complete the Adverse Events page

MEDICAL HISTORY / PHYSICAL EXAMINATION

Investigator's initials: _____

Please administer the study medication to the patient. ☐1 Given ☐2 Not given

History of (since previous visit)	No	Yes	If Yes, please comment
Night sweats	☐1	☐2	
Fever	☐1	☐2	
Cough	☐1	☐2	
Nausea/Vomiting	☐1	☐2	

Feeding: ☐1 Breast ☐2 Not breast. When was breast feeding stopped? |_|_|_|_|_|_| (give at least a month)
d d m m y y

	Normal	Abnormal*	Not done
General appearance	☐1	☐2	☐3
Skin	☐1	☐2	☐3
Eyes	☐1	☐2	☐3
Musculoskeletal	☐1	☐2	☐3
ENT	☐1	☐2	☐3

Heart rate : |_|_|_| beats/min Weight : |_|_|_| • |_|_| kg

Blood sample taken ? ☐1 No ☐2 Yes

* If abnormal, please complete the Adverse event page (Page 61).

COMPUTER NUMBER

Post-delivery 3 months: Infant | **LABORATORY DATA** | **Investigator's initials: _____**

Haematology No. _____	**Result***
Haemoglobin	
Haematocrit	
RBC - Erythrocytes	
Thrombocytes	
Total WBC - Leukocytes	
Lymphocytes	
Neutrophils	
Monocytes	
Eosinophils	
Basophils	
Other : _____	

Virology No. _____	**Result**
RPR	
CD4 counts	
CD8 counts	
CD4/CD8 ratio	
Plasma viral load	
ELISA/WB	
PCR	

* If the result is a clinically significant abnormality, please complete the Adverse Events page

PATIENT'S INITIALS	PATIENT NUMBER	HOSPITAL NUMBER

Post-delivery 9 months: Mother and Infant

INSTRUCTIONS

Please read the instructions carefully

1. Please record and complete the following:
   - Date of visit
   - Vital signs and Physical examination
2. Please take blood samples for laboratory measurements for mother and infant.
3. Administer the study medication to the mother and infant.
4. Make an appointment for the next visit when the baby is 12 months old.

PATIENT'S INITIALS	PATIENT NUMBER	HOSPITAL NUMBER

Post-delivery 9 months: Mother | **MEDICAL HISTORY** | **Investigator's initials:** _____

Date d d m m y y

History of (since previous visit)	No	Yes	If yes, please comment
General			
Night sweats	☐1	☐2	
Fever	☐1	☐2	
Cough	☐1	☐2	
Nausea / Vomiting	☐1	☐2	
Neurologic			
Headaches	☐1	☐2	
Confusion	☐1	☐2	

Post-delivery 9 months: Mother | **VITAL SIGNS AND PHYSICAL EXAMINATION** | **Investigator's initials:** _____

Measurement	Value :
Systolic BP (mmHg)	☐☐☐
Diastolic BP (mmHg)	☐☐☐
Heart rate (beats/min)	☐☐☐
Heart sounds : _____	
Other, specify : _____	

Please administer the study medication to the patient

☐1 **Given** ☐2 **Not given**

Weight : ☐☐☐ • ☐☐ **kg**

	Normal	Abnormal*	Not done
General (anemia jaundice)	☐1	☐2	☐3
Skin	☐1	☐2	☐3
ENT	☐1	☐2	☐3
LN	☐1	☐2	☐3
Respiratory examination	☐1	☐2	☐3
CVS examination	☐1	☐2	☐3
GIT examination	☐1	☐2	☐3
UG tract examination	☐1	☐2	☐3
CNS examination	☐1	☐2	☐3
Other abnormalities, specify:	☐1	☐2	☐3
_____	☐1	☐2	☐3
_____	☐1	☐2	☐3

* If abnormal, please complete the Adverse event page (Page 59).

MEDICAL HISTORY / PHYSICAL EXAMINATION

Investigator's initials: _____

Please administer the study medication to the patient. ☐1 **Given** ☐2 **Not given**

History of (since previous visit)	No	Yes	If Yes, please comment
Night sweats	☐1	☐2	
Fever	☐1	☐2	
Cough	☐1	☐2	
Nausea/Vomiting	☐1	☐2	

Feeding: ☐1 Breast ☐2 Not breast. When was breast feeding stopped? |_|_|_|_|_|_| (give at least a month)
d d m m y y

	Normal	Abnormal*	Not done
General appearance	☐1	☐2	☐3
Skin	☐1	☐2	☐3
Eyes	☐1	☐2	☐3
Musculoskeletal	☐1	☐2	☐3
ENT	☐1	☐2	☐3

Heart rate : |_|_|_| beats/min Weight : |_|_|_| • |_|_| kg

Blood sample taken ? ☐1 No ☐2 Yes

* If abnormal, please complete the Adverse event page (Page 61).

PATIENT'S INITIALS	PATIENT NUMBER	HOSPITAL NUMBER

Any visit: Mother

ADVERSE EVENTS

Investigator's initials: _____

Were there any adverse events ? ☐₂ **None** ☐₂ **Yes, please complete all sections below, cross check appropriate number**

Were there any adverse events considered serious including life threatening ? If Yes, specify which event(s) and report to the local offices immediately.

Adverse Event *Please list ONE event per line*	Nature *1 Non-serious 2 Serious***	Date and time of onset *(ddmmyy) (hh:mm)*	Date and time stopped *If ongoing update at next visit (ddmmyy) (hh:mm)*	Intensity *1 Mild 2 Moderate 3 Severe*	Relation to study drug *1 Definite 2 Likely 3 Unlikely 4 No*	Action taken *(Several statements are possible) 1 None 2 Study drug withdrawn 3 Study drug discontinued and restarted 4 Dose of study drug reduced 5 Dose of study drug subsequently increased 6 Concomitant therapy 7 Other, specify below**	Outcome of event *1 Recurrence 2 Resolved 3 Improved 4 Unchanged 5 Worsened 6 Death 7 Insufficient follow-up*
1.	1 2	:	:	1 2 3	1 2 3 4	1 2 3 4 5 6 7	1 2 3 4 5 6 7
2.	1 2	:	:	1 2 3	1 2 3 4	1 2 3 4 5 6 7	1 2 3 4 5 6 7
3.	1 2	:	:	1 2 3	1 2 3 4	1 2 3 4 5 6 7	1 2 3 4 5 6 7
4.	1 2	:	:	1 2 3	1 2 3 4	1 2 3 4 5 6 7	1 2 3 4 5 6 7

** ☐ death ☐ life-threatening ☐ in-patient hospitalisation or prolongation of existing hospitalisation
☐ persistent or significant disability/incapacity ☐ congenital anomaly ☐ complications at birth

* **Comments** _____

Investigator's signature _____ **Date:** d d m m y y

Any visit: Mother | **ADVERSE EVENTS (continued)** | **Investigator's initials:** _____

Adverse Event *Please list ONE event per line*	Nature *1 Non-serious* *2 Serious***	Date and time of onset *(ddmmyy) (hh:mm)*	Date and time stopped *If ongoing update at next visit* *(ddmmyy) (hh:mm)*	Intensity *1 Mild* *2 Moderate* *3 Severe*	Relation to study drug *1 Definite* *2 Likely* *3 Unlikely* *4 No*	Action taken *(Several statements are possible)* *1 None* *2 Study drug withdrawn* *3 Study drug discontinued and restarted* *4 Dose of study drug reduced* *5 Dose of study drug subsequently increased* *6 Concomitant therapy* *7 Other, specify below*	Outcome of event *1 Recurrence* *2 Resolved* *3 Improved* *4 Unchanged* *5 Worsened* *6 Death* *7 Insufficient follow-up*
5.	1 2	__ __ __ __ : __ __	__ __ __ __ : __ __	1 2 3	1 2 3 4	1 2 3 4 5 6 7	1 2 3 4 5 6 7
6.	1 2	__ __ __ __ : __ __	__ __ __ __ : __ __	1 2 3	1 2 3 4	1 2 3 4 5 6 7	1 2 3 4 5 6 7
7.	1 2	__ __ __ __ : __ __	__ __ __ __ : __ __	1 2 3	1 2 3 4	1 2 3 4 5 6 7	1 2 3 4 5 6 7
8.	1 2	__ __ __ __ : __ __	__ __ __ __ : __ __	1 2 3	1 2 3 4	1 2 3 4 5 6 7	1 2 3 4 5 6 7

** ☐ death ☐ life-threatening ☐ in-patient hospitalisation or prolongation of existing hospitalisation
☐ persistent or significantdisability/incapacity ☐ congenital anomaly/birth ☐ complications at birth

* **Comments** _____

Investigator's signature _____ **Date:** __ __ __ __ __ __
d d m m y y

PATIENT'S INITIALS	PATIENT NUMBER	HOSPITAL NUMBER

Any visit: Infant | **ADVERSE EVENTS** | **Investigator's initials:** _____

Were there any adverse events ? ☐₂ **None** ☐₂ **Yes, please complete all sections below, cross check appropriate number**

Were there any adverse events considered serious including life threatening ? If Yes, specify which event(s) and report to the local offices immediately.

Adverse Event *Please list ONE event per line*	Nature *1 Non-serious 2 Serious***	Date and time of onset *(ddmmyy) (hh:mm)*	Date and time stopped *If ongoing update at next visit (ddmmyy) (hh:mm)*	Intensity *1 Mild 2 Moderate 3 Severe*	Relation to study drug *1 Definite 2 Likely 3 Unlikely 4 No*	Action taken *(Several statements are possible) 1 None 2 Study drug withdrawn 3 Study drug discontinued and restarted 4 Dose of study drug reduced 5 Dose of study drug subsequently increased 6 Concomitant therapy 7 Other, specify below**	Outcome of event *1 Recurrence 2 Resolved 3 Improved 4 Unchanged 5 Worsened 6 Death 7 Insufficient follow-up*
1.	1 2	:	:	1 2 3	1 2 3 4	1 2 3 4 5 6 7	1 2 3 4 5 6 7
2.	1 2	:	:	1 2 3	1 2 3 4	1 2 3 4 5 6 7	1 2 3 4 5 6 7
3.	1 2	:	:	1 2 3	1 2 3 4	1 2 3 4 5 6 7	1 2 3 4 5 6 7
4.	1 2	:	:	1 2 3	1 2 3 4	1 2 3 4 5 6 7	1 2 3 4 5 6 7

** ☐ death ☐ life-threatening ☐ in-patient hospitalisation or prolongation of existing hospitalisation
☐ persistent or significant disability/incapacity ☐ congenital anomaly ☐ complications at birth

* **Comments** _____

Investigator's signature _____ **Date:** d d m m y y

Any visit: Infant | **ADVERSE EVENTS (continued)** | **Investigator's initials:** _____

Adverse Event *Please list ONE event per line*	Nature *1 Non-serious* *2 Serious***	Date and time of onset *(ddmmyy) (hh:mm)*	Date and time stopped *If ongoing update at next visit* *(ddmmyy) (hh:mm)*	Intensity *1 Mild* *2 Moderate* *3 Severe*	Relation to study drug *1 Definite* *2 Likely* *3 Unlikely* *4 No*	Action taken *(Several statements are possible)* *1 None* *2 Study drug withdrawn* *3 Study drug discontinued and restarted* *4 Dose of study drug reduced* *5 Dose of study drug subsequently increased* *6 Concomitant therapy* *7 Other, specify below**	Outcome of event *1 Recurrence* *2 Resolved* *3 Improved* *4 Unchanged* *5 Worsened* *6 Death* *7 Insufficient follow-up*
5.	1 2	__ __ __ __ : __ __	__ __ __ __ : __ __	1 2 3	1 2 3 4	1 2 3 4 5 6 7	1 2 3 4 5 6 7
6.	1 2	__ __ __ __ : __ __	__ __ __ __ : __ __	1 2 3	1 2 3 4	1 2 3 4 5 6 7	1 2 3 4 5 6 7
7.	1 2	__ __ __ __ : __ __	__ __ __ __ : __ __	1 2 3	1 2 3 4	1 2 3 4 5 6 7	1 2 3 4 5 6 7
8.	1 2	__ __ __ __ : __ __	__ __ __ __ : __ __	1 2 3	1 2 3 4	1 2 3 4 5 6 7	1 2 3 4 5 6 7

** ☐ death ☐ life-threatening ☐ in-patient hospitalisation or prolongation of existing hospitalisation
☐ persistent or significantdisability/incapacity ☐ congenital anomaly/birth ☐ complications at birth

* **Comments** _____

Investigator's signature _____ **Date:** __ __ __ __ __ __ (d d m m y y)

Premature termination: Mother | **VITAL SIGNS AND PHYSICAL EXAMINATION** | **Investigator's initials:** _____

Date of termination: ☐☐ ☐☐ ☐☐ (d d m m y y)

Weight : ☐☐☐ • ☐☐ kg

Measurement	Value :
Systolic BP (mmHg)	☐☐☐
Diastolic BP (mmHg)	☐☐☐
Heart rate (beats/min)	☐☐☐
Heart sounds : _____	
Other, specify : _____	

	Normal	Abnormal*	Not done
General (anemia jaundice) ☐1	☐2	☐3	
Skin ☐1	☐2	☐3	
ENT ☐1	☐2	☐3	
LN ☐1	☐2	☐3	
Respiratory examination ☐1	☐2	☐3	
CVS examination ☐1	☐2	☐3	
GIT examination ☐1	☐2	☐3	
UG tract examination ☐1	☐2	☐3	
CNS examination ☐1	☐2	☐3	
Other abnormalities, specify: ☐1	☐2	☐3	
_____ ☐1	☐2	☐3	
_____ ☐1	☐2	☐3	

* If abnormal, please complete the Adverse event page (Page 59).

COMPUTER NUMBER

Premature termination: Mother | **LABORATORY DATA** | **Investigator's initials: _____**

Haematology No. _____	**Result***
Haemoglobin	
Haematocrit	
RBC - Erythrocytes	
Thrombocytes	
Total WBC - Leukocytes	
Lymphocytes	
Neutrophils	
Monocytes	
Eosinophils	
Basophils	
Other : _____	

Virology No. _____	**Result**
RPR	
CD4 counts	
CD8 counts	
CD4/CD8 ratio	
Plasma viral load	
Milk viral load	

* If the result is a clinically significant abnormality, please complete the Adverse Events page

Premature termination: Infant | **VITAL SIGNS AND PHYSICAL EXAMINATION** | **Investigator's initials: _____**

Date of termination: ☐☐ ☐☐ ☐☐ (d d m m y y)

History of (since previous visit)	No	Yes	If Yes, please comment
Night sweats	☐1	☐2	
Fever	☐1	☐2	
Cough	☐1	☐2	
Nausea/Vomiting	☐1	☐2	

Feeding: ☐1 Breast ☐2 Not breast. When was breast feeding stopped? ☐☐ ☐☐ ☐☐ (d d m m y y) (give at least a month)

	Normal	Abnormal*	Not done
General appearance	☐1	☐2	☐3
Skin	☐1	☐2	☐3
Eyes	☐1	☐2	☐3
Musculoskeletal	☐1	☐2	☐3
ENT	☐1	☐2	☐3

Heart rate : ☐☐☐ beats/min Weight : ☐☐☐ • ☐☐ kg

Blood sample taken ? ☐1 No ☐2 Yes

* If abnormal, please complete the Adverse event page (Page 61).

COMPUTER NUMBER

Premature termination: Infant | **LABORATORY DATA** | **Investigator's initials: _____**

Haematology No. _____	**Result***
Haemoglobin	
Haematocrit	
RBC - Erythrocytes	
Thrombocytes	
Total WBC - Leukocytes	
Lymphocytes	
Neutrophils	
Monocytes	
Eosinophils	
Basophils	
Other : _____	

Virology No. _____	**Result**
RPR	
CD4 counts	
CD8 counts	
CD4/CD8 ratio	
Plasma viral load	
ELISA/WB	
PCR	

* If the result is a clinically significant abnormality, please complete the Adverse Events page

PATIENT'S INITIALS	PATIENT NUMBER	HOSPITAL NUMBER

Any visit: Post-delivery

OTHER MEDICATION

Investigator's initials: _____

Other medication ? ☐ 1 **No** ☐ 2 **Yes**

If yes, give details:

Description	Trade Name	Daily dose administered	Date started (dd/mm/yy)	Date stopped (dd/mm/yy)

PATIENT'S INITIALS	PATIENT NUMBER	HOSPITAL NUMBER

STUDY TERMINATION FORM

Investigator's initials: _____

Was the study terminated prematurely for this patient? ☐1 **No** ☐2 **Yes, please specify :**

Date : d d m m y y

The study was terminated due to the following reasons :

- ☐1 **Adverse event (see adverse events form)**
- ☐2 **Patient non-compliance**
- ☐3 **Consent withdrawn**
- ☐4 **Patient lost to follow-up**
- ☐5 **Death**
- ☐6 **Baby eighteen months old**
- ■ **Other, please specify :** _____

Comments _____

_____

Investigator's signature _____ **Date :** d d m m y y

PATIENT'S INITIALS	PATIENT NUMBER	HOSPITAL NUMBER

STUDY MEDICATION RECORD

Investigator's initials: _____

Visit dispensed	Date dispensed *(ddmmyy)*	Number of tablets dispensed	Date returned *(ddmmyy)*	Number of tablets returned
1				
2				
3				
Premature Withdrawal				

APPENDIX 6

Patient diary card

Instructions

The pages of the diary were provided for the appropriate months of the phase one period of the study.

PATIENT'S INITIALS	PATIENT NUMBER	HOSPITAL NUMBER

PATIENT DIARY CARD

Investigator's name : _____

Place of work : _____

Contact Telephone :_____

PATIENT'S INITIALS	PATIENT NUMBER	HOSPITAL NUMBER

Visit 1

INSTRUCTIONS

Please complete the following each day when you take your study medication

January															
Did you take medication from the packet today ? If **Yes**, please tick (✓) for the appropriate day.															
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	

February															
Did you take medication from the packet today ? If **Yes**, please tick (✓) for the appropriate day.															
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
17	17	19	20	21	22	23	24	25	26	27	28				

PATIENT'S INITIALS	PATIENT NUMBER	HOSPITAL NUMBER

Visit 1

INSTRUCTIONS

Please complete the following each day when you take your study medication

March															
Did you take medication from the packet today ? If **Yes**, please tick (✓) for the appropriate day.															
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	

April															
Did you take medication from the packet today ? If **Yes**, please tick (✓) for the appropriate day.															
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
17	17	19	20	21	22	23	24	25	26	27	28	29	30		

APPENDIX 7

Patient's appointment card

VITAMIN A STUDY

Next visit date:_____ Time_____

Place:_____

Perpetual Chikobvu

Tel: (051) 401-3117

Fax: (051) 401-2939

Unversity of the Free State

Faculty of Health Sciences

Bloemfontein 9300

cc Dr E van der Ryst

Tel: (051) 405-3162

or

Dr WJ Steinberg

Tel:(051) 405-3448

APPENDIX 8

Patient's transfer (referral) letter

Instructions

A similar letter was addressed to Sister Steyn at Universitas hospital

DIE UNIVERSITEIT VAN DIE ORANJE-VRYSTAAT

Departement Biostatistiek
Fakulteit Geneeskunde

✉ 339 BLOEMFONTEIN 9300
☎ (051) 4013114/5/6/7

REPUBLIEK VAN SUID-AFRIKA
FAKS (051) 4471779

VITAMIN A STUDY

Attention: Sister Jikila

Immunology Clinic

Pelonomi Hospital

Phone 4051655

Dear Sister,

I hereby refer _____, a patient for the vitamin

A study (study number _____and expected date of delivery:

_____) to immunology clinic situated on the 3rd floor in 'Special Block' at

Pelonomi Hospital. Date of appointment: _____

Yours

_____ |_____|
Signature Date

APPENDIX 9

Minutes of 1st and 2nd blind review meetings and infants HIV results

Minutes of 1st data review Meeting: UFS Vitamin A study

Date: 9th February 2001
Time: 11 am
Present: Professor G Joubert
Dr R Schall
Dr JI Viljoen
WJ Steinberg
Ms P Chikobvu

Definition of analysis populations

The analysis populations were defined in the study statistical analysis plan (Section 4).
During the review, the following clarifications of those definitions were made.

Safety population

Exclusion criteria from safety population:
Patients who did not receive randomised study medication

Intention-to-treat (ITT) population

Exclusion criteria from ITT population:
All Patients without at least one conclusive result on HIV status of the infant based on either PCR or p-24 antigen test or an Elisa antibody test.

Per-protocol (PP) population

Exclusion criteria from PP Population:
All Patients without conclusive HIV results for infants based on PCR test at 3 months.
Major protocol violations:

Modification of statistical analysis plan

Dr Viljoen distributed the literature for the use of PCR and P-24 antigen HIV tests. It was then agreed that when a p-24antigen HIV test result contradicts a PCR HIV result at any time a PCR test result is considered.

Analysis populations

Exclusions from the various analysis populations are listed on the "Infant HIV results list" below. Infant HIV results of other patients were agreed upon except for 27 patients (See infant HIV results list below, column written "First Review Results") where a re-test (depending on availability of blood) using either PCR

and/or Elisa antibody test was agreed upon. It was also agreed that patient number 250 would be excluded when calculating the transmission rates. The second Blind review meeting was to be held as soon as these HIV results will be available.
The analysis populations agreed upon include the following numbers of Patients:
Total Patients reviewed: n = 304 (this includes one twin);
Total Patients randomised: n = 303;
Safety population: n =303 mothers and 171 infants.
Intention to treat population: n = to be given after the 2nd review meeting
Per-protocol population: n = to be given after the 2nd review meeting
The meeting closed at 12.15 pm.

Minutes of 2nd data review Meeting: UFS Vitamin A study

Date: 12th June 2001
Time: 11 am
Present: Professor G Joubert
Dr R Schall
Dr JI Viljoen
WJ Steinberg
Ms P Chikobvu

Modification of statistical analysis plan

If a PCR contradicts an ELISA test on the blood drawn the same day then the result will be considered as conflicting and the patient will be excluded from both ITT and PP analysis populations when calculating transmission rates.

Analysis populations

Infant HIV results of all the re-tests were agreed upon (See infant HIV results list below). It was also agreed that patient number 8 would be excluded when calculating the transmission rates.
The analysis populations agreed upon include the following numbers of patients:
Intention to treat population: n = 158
Per-protocol population: n = 104
The meeting closed at 12.pm.

Definitions used for the Infant HIV results table below

Result at NIV → blood was tested at the National Institute for Virology.
ELISA and P-24 UFS → blood was tested at the University of the Free State. ; PCR UCT → blood was tested at the University of Cape town.
PCR NIV → blood was testd at the National Institute for Virology. ; 3/12 → blood was drawn when the infant was between 1 and 4 months old.
>3/12 → blood was drawn when the infant was 4 months old or more.; >=15/12 → blood was drawn when the infant was 15 months old or more.
Pat no → patient number ; DOB → date of birth for the infant.; BA, BB, BC, BD, BE → 1st , 2nd 3

INFANT HIV RESULTS LIST

Pat no	DOB	P-24 1/12 UFS	P-24 3/12 UFS	P-24 6/12 UFS	P-24 12/12 UFS	P-24 >=15/12 UFS	PCR 3/12 UCT	PCR >3/12 UCT	PCR 3/12 NIV	PCR >3/12 NIV	First Review Results	ELISA .>=15/12 UFS	New PCR 3/12 UCT	New PCR >3/12 UCT	Final Result & analysis Population
1	IUD														
2	06/03/98		BA Serum 18/05/98 negative at NIV	BB Serum 07/09/98 negative at NIV			BA 18/5/98 Negative			BB 7/9/98 Negative	Negative	BD 13/9/99 Negative			Negative PP & ITT
3	None														
4	None														
5	None														
6	Expected Date 6/1/98				BA* Serum 14/04/99 negative at NIV	BA* Heparin 14/04/99 negative				BA 14/4/99 Positive	Positive				Positive ITT
7	02/12/98	BA Serum 04/03/98 negative at NIV	BB Serum 03/06/98 negative at NIV				BA 4/3/98 Negative			BA 4/3/98 Negative	Negative				Negative PP & ITT
8	Expected Date 17/2/98					BA Heparin Plasma 12/7/99 negative					Re-test	BA 12/7/99 Negative		BA 12/7/99 Positive	Conflicting NONE
9	30/12/97		BA Serum 20/04/98 positive at NIV	BB Serum 13/07/98 positive at NIV					BA 20/4/98 Positive	BB 13/7/98 Positive	Positive				Positive PP & ITT
10	04/11/97						BA 4/2/98 Insufficient Blood				Re-test			BB 6/5/98 Negative	Negative ITT

Pat no	DOB	P-24 1/12 UFS	P-24 3/12 UFS	P-24 6/12 UFS	P-24 12/12 UFS	P-24 >=15/12 UFS	PCR 3/12 UCT	PCR >3/12 UCT	PCR 3/12 NIV	PCR >3/12 NIV	First Review Results	ELISA .>=15/12 UFS	New PCR 3/12 UCT	New PCR >3/12 UCT	Final result & analysis population
11	16/01/98		BA Serum 20/04/98 negative at NIV	BB Serum 20/07/98 negative at NIV	BC Serum 08/02/99 negative at NIV		BA 20/4/98 Negative			BC 8/2/99 Negative	Negative				Negative PP & ITT
12	12/10/97		BA Serum 19/01/98 negative				BA 19/1/98 Insufficient Blood				Re-test		BA 19/1/98 Positive		Positive PP & ITT
13	07/02/98		BA Serum 1/4/98 negative at NIV	BB Serum 17/08/98 negative at NIV	BC Serum 01/03/99 negative at NIV		BA 1/4/98 Negative			BC 1/3/99 Negative	Negative	BD 30/8/99 Negative			Negative PP & ITT
14	20/10/97	BA Serum 24/11/97 negative at NIV	BB Serum 19/01/98 negative at NIV	BC Serum 20/04/98 negative at NIV	BD Serum 26/10/98 negative at NIV		BB 19/1/98 Insufficient Blood			BD 26/10/98 Indeterminant Result	Re-test		BB 19/1/98 Negative		Negative PP & ITT
15	03/10/97	BA EDTA 05/11/97 negative at NIV		BC Serum 15/04/98 negative at NIV			BB 19/1/98 Negative			BC 15/4/98 Indeterminant Result	Negative	BE 28/7/99 Negative			Negative PP & ITT
16	None														
17	12/11/97		BA Serum 18/02/98 negative at NIV	BB Serum 13/05/98 negative at NIV	BC Serum 18/11/98 negative at NIV		BA 18/2/98 Negative			BC 18/11/98 Negative	Negative				Negative PP & ITT

Pat no	DOB	P-24 1/12 UFS	P-24 3/12 UFS	P-24 6/12 UFS	P-24 12/12 UFS	P-24 >=15/12 UFS	PCR 3/12 UCT	PCR >3/12 UCT	PCR 3/12 NIV	PCR >3/12 NIV	First Review Results	ELISA .>=15/12 UFS	New PCR 3/12 UCT	New PCR >3/12 UCT	Final result & analysis population
18	12/04/98		BA Serum 13/07/98 negative	BB Serum 12/10/98 negative	BC Serum 19/04/99 negative	BD Serum 18/10/99 negative	BA 13/7/98 Positive				Re-test	BD 18/10/99 Positive		BC 19/4/99 Positive	Positive PP & ITT
19	None														
20	14/01/98		BA Serum 20/04/98 negative at NIV	BB EDTA 27/07/98 positive at NIV	BC Serum 01/02/99 negative at NIV	BD Serum 19/04/99 negative	BA 20/4/98 Negative			BC 1/2/99 Indeterminant Result	Negative	BD 19/4/99 Negative			Negative PP & ITT
21	None														
22	10/2/98				BA Serum 03/05/99 negative						Re-test			BA 3/5/99 Negative	Negative ITT
23	None														
24	None														
25	None														
26	None														
27	29/11/97		BA Serum 30/03/98 negative at NIV							BA 30/3/98 Positive	Positive				Positive ITT
28	27/11/97		BA Serum 23/02/98 positive at NIV						BA 23/2/98 Positive		Positive				Positive PP & ITT
29	None														
30	None														
31	None														
32	None														

Pat no	DOB	P-24 1/12 UFS	P-24 3/12 UFS	P-24 6/12 UFS	P-24 12/12 UFS	P-24 >=15/12 UFS	PCR 3/12 UCT	PCR >3/12 UCT	PCR 3/12 NIV	PCR >3/12 NIV	First Review Results	ELISA .>=15/12 UFS	New PCR 3/12 UCT	New PCR >3/12 UCT	Final result & analysis population
33	None														
34	07/01/98				BA Serum 15/02/99 negative	BB Serum 17/05/99 negative					Re-test	BC 12/7/99 Negative		BD 12/7/99 Negative	Negative ITT
35	05/03/98		BA Serum 25/05/98 negative at NIV	BB EDTA 09/09/98 negative at NIV			BA 25/5/98 Negative			BB 9/9/98 Negative	Negative				Negative PP & ITT
36	04/11/97		BA Serum 09/03/98 negative at NIV	BB Serum 04/05/98 negative at NIV	BC Serum 09/11/98 negative at NIV			BA 9/3/98 Negative		BC 9/11/98 Indeterminant Result	Negative	BD 10/5/99 Negative			Negative ITT
37	19/12/97	Baby Received Medicine	No blood* Patient's Request 25/03/98												
38	16/02/98		BA Serum 18/05/98 negative at NIV	BB Serum 17/08/98 negative at NIV	BC Serum 22/02/99 negative at NIV		BA 18/5/98 Negative			BC 22/2/99 Indeterminant Result	Negative				Negative PP & ITT
39	14/01/98		BA Serum 29/04/98 negative at NIV	BB Serum 22/02/98 negative at NIV	BC Serum 03/02/99 positive at NIV	BC EDTA 03/02/99 positive	BA 29/4/98 Insufficient Blood			BC 3/2/99 Negative	Re-test	BE 12/7/99 Negative		BE 12/7/99 Negative	Negative ITT
40	22/11/97	Baby died no Medicine													
41	None														

Pat no	DOB	P-24 1/12 UFS	P-24 3/12 UFS	P-24 6/12 UFS	P-24 12/12 UFS	P-24 >=15/12 UFS	PCR 3/12 UCT	PCR >3/12 UCT	PCR 3/12 NIV	PCR >3/12 NIV	First Review Results	ELISA .>=15/12 UFS	New PCR 3/12 UCT	New PCR >3/12 UCT	Final result & analysis population
42	None														
43	None														
44	04/03/98		BA Serum 08/06/98 negative	BB Serum 07/09/98 negative			BA 8/6/98 Negative				Negative	BD 13/9/99 Negative			Negative PP & ITT
45	16/01/98		BA Serum 20/04/98 negative at NIV	BB Serum 20/07/98 negative at NIV	BC Serum 08/02/99 positive at NIV	BD Serum 19/04/99 positive	BA 20/4/98 Negative			BC 8/2/99 Positive	Negative & Positive After 3 months	BD 19/7/99 Positive			Negative & Positive after 3 months PP & ITT
46	None														
47	None														
48	None														
49	None														
50	None														
51	None														
52	05/02/98			BA Serum 17/08/98 positive at NIV	BB Serum 22/02/99 positive at NIV	BC* Serum 03/05/99 negative		BA 17/8/98 Positive		BB 22/2/99 Positive	Positive	BD 2/8/99 Positive			Positive ITT
53	None														
54	15/02/98		BA Serum 18/05/98 negative at NIV	BB Serum 17/08/98 negative at NIV			BA 18/5/98 Negative			BB 17/8/99 Indeterminant Result	Negative				Negative PP & ITT
55	None														
56	24/02/98		BA Serum 01/06/98 negative at NIV	BB Serum 24/08/98 negative at NIV			BA 1/6/98 Negative			BB 24/8/98 Negative	Negative				Negative PP & ITT

Pat no	DOB	P-24 1/12 UFS	P-24 3/12 UFS	P-24 6/12 UFS	P-24 12/12 UFS	P-24 >=15/12 UFS	PCR 3/12 UCT	PCR >3/12 UCT	PCR 3/12 NIV	PCR >3/12 NIV	First Review Results	ELISA .>=15/12 UFS	New PCR 3/12 UCT	New PCR >3/12 UCT	Final result & analysis population
57	08/03/98				BA Serum 22/02/99 negative						Re-test			BA 22/2/99 Negative	Negative ITT
58	None														
59	31/3/98				BA Serum 14/6/99 negative						Re-test			BA 14/6/99 Negative	Negative ITT
60	01/04/98			BB Serum 05/10/98 negative		BD Serum 4/10/99 negative	BA 27/7/98 Negative				Negative	BD 4/10/99 Negative			Negative PP & ITT
61	None														
62	None														
63	None														
64	08/05/98		BA Serum 17/08/98 negative	BB Serum 09/11/98 negative	BC Serum 10/05/99 negative	BD Serum 15/11/99 negative	BA 17/8/98 Negative				Negative	BD 15/11/99 Negative			Negative PP & ITT
65	16/04/98		BA Serum 20/07/98 negative	BB Serum 19/10/98 negative	BC Serum 19/04/99 negative	BD Serum 18/10/99 negative	BA 20/7/98 Negative				Negative	BD 18/10/99 Negative			Negative PP & ITT
66	None														
67	None														
68	24/05/98		BA* EDTA 09/10/98 negative	BB Serum 25/11/98 negative		BD Serum 3/11/99 negative		BA 9/10/98 Negative			Negative	BD 3/11/99 Negative			Negative ITT

Pat no	DOB	P-24 1/12 UFS	P-24 3/12 UFS	P-24 6/12 UFS	P-24 12/12 UFS	P-24 >=15/12 UFS	PCR 3/12 UCT	PCR >3/12 UCT	PCR 3/12 NIV	PCR >3/12 NIV	First Review Results	ELISA .>=15/12 UFS	New PCR 3/12 UCT	New PCR >3/12 UCT	Final result & analysis population
69	03/04/98			BB Serum 05/10/98 negative	BC Serum 12/04/99 negative	BD Serum 11/10/99 negative		BA 17/8/98 Negative			Negative	BD 11/10/99 Negative			Negative ITT
70	None														
71	None														
72	26/01/98	Baby Received Medicine													
73	None														
74	None														
75	25/04/98		BA Serum 03/08/98 negative	BB Serum 02/11/98 negative	BC Serum 26/04/99 negative		BA 3/8/98 Positive				Positive	BD 25/10/99 Positive			Positive PP & ITT
76	19/06/98	Baby* Died no Medicine													
77	None														
78	10/02/98				BA Serum 24/02/99 negative						Re-test			BA 24/2/99 Negative	Negative ITT
79	30/06/98			BB Serum 13/1/99 negative			BA 14/10/98 Negative				Negative	BD 22/10/99 Negative			Negative PP & ITT
80	None														
81	None														
82	03/03/98		BA Serum 08/06/98 negative	BB Serum 07/09/98 negative			BA 8/6/98 Negative				Negative	BD 13/9/99 Negative			Negative PP & ITT
83	None														

Pat no	DOB	P-24 1/12 UFS	P-24 3/12 UFS	P-24 6/12 UFS	P-24 12/12 UFS	P-24 >=15/12 UFS	PCR 3/12 UCT	PCR >3/12 UCT	PCR 3/12 NIV	PCR >3/12 NIV	First Review Results	ELISA .>=15/12 UFS	New PCR 3/12 UCT	New PCR >3/12 UCT	Final result & analysis population
84	21/05/98		BA Serum 24/08/98 negative at NIV	BB Serum 23/11/98 positive at NIV		BD Serum 15/11/99 negative			BA 24/8/98 negative	BB 23/11/98 Positive	Negative & Positive After 3 months	BD 15/11/99 Positive		BC 24/5/99 Positive	Negative & Positive after 3 months PP & ITT
85	None														
86	16/06/98		BA Serum 21/9/98 negative	BB Serum 25/01/99 Negative	BC Serum 21/06/99 negative		BA 21/9/98 Negative				Negative	BD 24/1/00 Negative			Negative PP & ITT
87	18/04/98		BA Serum 03/08/98 negative	BB Serum 19/10/98 negative	BC Serum 19/4/99 negative		BA 3/8/98 Negative				Negative	BD 18/10/99 Negative			Negative PP & ITT
88	Expected Date 21/3/98				BA Serum 7/6/99 negative						Re-test			BA 7/6/99 Negative	Negative ITT
89	None														
90	24/o4/98		BA Serum 03/08/98 negative	BB Serum 26/10/98 negative	BC Serum 26/04/99 negative	BD Serum 1/1199 negative	BA 3/8/98 Negative				Negative	BD 1/11/99 Negative			Negative PP & ITT
91	20/05/98							BA 24/8/98 Negative			Negative				Negative ITT
92	02/05/98	Medicine Received													
93	None														
94	None														
95	11/06/98	Medicine Received													
96	None														
97	None														

Pat no	DOB	P-24 1/12 UFS	P-24 3/12 UFS	P-24 6/12 UFS	P-24 12/12 UFS	P-24 >=15/12 UFS	PCR 3/12 UCT	PCR >3/12 UCT	PCR 3/12 NIV	PCR >3/12 NIV	First Review Results	ELISA .>=15/12 UFS	New PCR 3/12 UCT	New PCR >3/12 UCT	Final result & analysis population
98	28/05/98			BB Serum 18/01/99 negative			BA 7/9/98 Negative				Negative	BD 10/1/00 Negative			Negative PP & ITT
99	17/05/98										Re-test		BA 19/8/98 Negative		Negative PP & ITT
100	26/4/98				BA Serum 15/02/99 21/06/99 negative						Re-test			BA 15/2/99 Negative	Negative ITT
101	None														
102	None														
103	15/05/98				BC Serum 17/05/99 negative	BD Serum 22/11/99 negative	BA 17/8/98 Negative				Negative	BD 15/11/99 Negative			Negative PP & ITT
104	None														
105	None														
106	25/05/98		BA Serum 31/08/98 positive at NIV				BA 31/8/98 Positive		BA 31/8/98 Positive		Positive				Positive PP & ITT
107	08/08/98		BA Serum 14/09/98 positive at NIV				BA 14/9/98 Positive		BA 14/9/98 Positive		Positive				Positive PP & ITT
108	None														
109	None														
110	None														

Pat no	DOB	P-24 1/12 UFS	P-24 3/12 UFS	P-24 6/12 UFS	P-24 12/12 UFS	P-24 >=15/12 UFS	PCR 3/12 UCT	PCR >3/12 UCT	PCR 3/12 NIV	PCR >3/12 NIV	First Review Results	ELISA .>=15/12 UFS	New PCR 3/12 UCT	New PCR >3/12 UCT	Final result & analysis population
111	30/5/98				BA Serum 1/3/99 negative						Re-test			BA 1/3/99 Negative	Negative ITT
112	None														
113	21/5/98				BA EDTA Plasma 14/6/99 negative						Re-test			BA 14/6/99 Negative	Negative ITT
114	23/06/98		BA Serum 23/9/98 negative	BB Serum 27/1/99 negative	BC Serum 30/9699 negative		BA 23/9/98 Negative				Negative	BD 24/1/00 Negative			Negative PP & ITT
115	None														
116	08/04/98		BA Serum 13/07/98 negative	BB Serum 12/10/98 negative	BC Serum 12/04/99 negative		BA 13/7/98 Negative				Negative	BD 4/10/99 Negative			Negative PP & ITT
117	None														
118	None														
119	None														
120	None														
121	07/06/98		BA Serum 21/09/98 negative	BB Serum 20/01/99 negative			BA 21/9/98 Negative				Negative				Negative PP & ITT
122	None														

Pat no	DOB	P-24 1/12 UFS	P-24 3/12 UFS	P-24 6/12 UFS	P-24 12/12 UFS	P-24 >=15/12 UFS	PCR 3/12 UCT	PCR >3/12 UCT	PCR 3/12 NIV	PCR 3/12 NIV	First Review Results	ELISA .>=15/12 UFS	New PCR 3/12 UCT	New PCR >3/12 UCT	Final result & analysis population
123	20/06/98		BA Serum 09/09/98 positive at NIV			BD Serum 19/1/00 negative	BA 9/9/98 Positive		BA 9/9/98 Positive	BB 31/3/99 Positive	Positive	BD 19/1/00 Positive			Positive PP & ITT
124	None														
125	29/06/98		BA Serum 30/9/98 negative	BB Serum 27/1/99 negative	BC Serum 30/6/99 negative		BA 30/9/98 Negative				Negative	BD 31/1/00 Negative			Negative PP & ITT
126	23/07/98		BA Heparin Plasma 2/11/98 negative	BB Serum 15/2/99 negative			BA 2/11/98 Negative				Negative				Negative PP & ITT
127	None														
128	None														
129	None														
130	None														
131	None														
132	None														
133	None														
134	None														
135	10/07/98		BA Serum 14/10/98 positive	BB Serum 3/2/99 positive			BA 14/10/98 Positive				Positive				Positive PP & ITT
136	None														

Pat no	DOB	P-24 1/12 UFS	P-24 3/12 UFS	P-24 6/12 UFS	P-24 12/12 UFS	P-24 >=15/12 UFS	PCR 3/12 UCT	PCR >3/12 UCT	PCR 3/12 NIV	PCR >3/12 NIV	First Review Results	ELISA .>=15/12 UFS	New PCR 3/12 UCT	New PCR >3/12 UCT	Final result & analysis population
137	None														
138	7/798		BA Serum 14/10/98 negative	BB Serum 3/2/99 negative	BC Serum 21/7/99 Negative		BA 14/10/98 Negative				Negative	BD 21/2/00 Negative			Negative PP & ITT
139	None														
140	None														
141	01/06/98		BA Serum 07/09/98 negative	BB Serum 18/01/99 negative			BA 7/9/98 Negative				Negative	BD 10/1/00 Negative			Negative PP & ITT
142	Expected Date 10/6/98				BA Serum 31/5/99 negative						Re-test			BA 31/5/99 Negative	Negative ITT
143	None														
144	23/07/98		BA Serum No date negative	BB Serum 22/2/99 negative			BA 2/11/98 Negative				Negative				Negative PP & ITT
145	None														
146	22/08/98			BA Serum 26/4/99 negative	BB Serum 6/9/99 negative			BA 26/4/99 Negative			Negative	BC 21/2/00 Negative			Negative ITT
147	None														
148	None														
149	02/09/98		BA Serum 28/10/98 negative		BC Serum 15/9/99 Negative			BB 27/1/99 Negative			Negative				Negative ITT

Pat no	DOB	P-24 1/12 UFS	P-24 3/12 UFS	P-24 6/12 UFS	P-24 12/12 UFS	P-24 >=15/12 UFS	PCR 3/12 UCT	PCR >3/12 UCT	PCR 3/12 NIV	PCR >3/12 NIV	First Review Results	ELISA .>=15/12 UFS	New PCR 3/12 UCT	New PCR >3/12 UCT	Final result & analysis population
150	None														
151	21/7/98			BA Serum 26/04/99 negative							Re-test			BA 26/4/99 Positive	Positive ITT
152	None														
153	21/01/99		BA Serum 17/3/99 negative	BB Serum 9/6/99 negative				BA 17/3/99 Negative			Negative				Negative ITT
154	30/08/98		BA Serum 25/1/99 negative	BA Serum 1/3/99 negative	BC Serum 27/9/99 negative			BA 25/1/99 Negative			Negative	BD 10/4/00 Negative			Negative ITT
155	30/07/98			BA Serum 8/2/99 negative	BC Serum 2/8/99 negative			BA 8/2/99 Negative			Negative	BD 28/2/00 Negative			Negative ITT
156	24/7/98			BA Serum 26/04/99 negative							Re-test			BA 26/4/99 Negative	Negative ITT
157	18/07/98		BA Heparin plasma 28/10/98 negative	BB Serum 27/1/99 negative	BC Serum 21/7/99 negative		BA 28/10/98 Negative				Negative	BD 14/2/00 Negative			Negative PP & ITT
158	None														

Pat no	DOB	P-24 1/12 UFS	P-24 3/12 UFS	P-24 6/12 UFS	P-24 12/12 UFS	P-24 >=15/12 UFS	PCR 3/12 UCT	PCR >3/12 UCT	PCR 3/12 NIV	PCR >3/12 NIV	First Review Results	ELISA .>=15/12 UFS	New PCR 3/12 UCT	New PCR >3/12 UCT	Final result & analysis population
159	23/06/98		BA Serum 30/9/98 negative	BB Serum 27/1/99 negative	BC Serum 7/7/99 negative		BA 30/9/98 Negative				Negative	BD 7/2/00 Negative			Negative PP & ITT
160	16/7/98						BA 28/9/98 Negative				Negative				Negative PP & ITT
161	06/07/98		BA Serum 12/10/98 negative	BB Serum 1/2/99 negative	BC Serum 12/7/99 negative		BA 12/10/98 Negative				Negative	BD 14/2/00 Negative			Negative PP & ITT
162	7/9/98		BA Serum 11/1/99 negative								Re-test			BA 11/1/99 Negative	Negative ITT
163	None														
164	None														
165	06/09/98	Medicine Received													
166	04/10/98		BA Serum 13/1/99 negative	BB Serum 7/4/99 negative	BC Serum 6/10/99 negative		BA 13/1/99 Negative				Negative	BD 17/4/00 Negative			Negative PP & ITT
167	None														
168	None														
169	None														
170	None														
171	03/09/98		BA Serum 15/2/99 negative	BB Serum 12/4/99 negative	BC Serum 6/9/99 Negative		BA 15/2/99 Negative				Negative	BD 20/3/00 Negative			Negative PP & ITT

Pat no	DOB	P-24 1/12 UFS	P-24 3/12 UFS	P-24 6/12 UFS	P-24 12/12 UFS	P-24 >=15/12 UFS	PCR 3/12 UCT	PCR >3/12 UCT	PCR 3/12 NIV	PCR >3/12 NIV	First Review Results	ELISA .>=15/12 UFS	New PCR 3/12 UCT	New PCR >3/12 UCT	Final result & analysis population
172	05/08/98	Medicine Receive													
173	None														
174	18/8/98		BA Serum 18/1/99 negative	BB Serum 15/3/99 negative	BC Serum 13/9/99 negative			BA 18/1/99 Negative			Negative	BD 21/2/00 Negative			Negative ITT
175	04/09/98		BA Serum 11/1/99 negative	BB Serum 8/3/99 negative	BC Serum 13/9/99 negative		BA 11/1/99 positive				Positive				Positive PP & ITT
176	None														
177	None														
178	28/07/98		BA Serum 23/11/98 negative	BB Serum 15/2/99 negative	BC Serum 2/8/99 negative		BA 23/11/98 Negative				Negative	BD 28/2/00 Positive			Negative & Positive after 3 months PP & ITT
179	04/09/98			BA Serum 15/3/99 negative	BB Serum 6/9/99 negative			BA 15/3/99 Negative			Negative				Negative ITT
180	None														
181	None														
182	06/09/98		BA Serum 27/1/99 negative				BA 27/1/99 Negative				Negative				Negative PP & ITT
183	None														

Pat no	DOB	P-24 1/12 UFS	P-24 3/12 UFS	P-24 6/12 UFS	P-24 12/12 UFS	P-24 >=15/12 UFS	PCR 3/12 UCT	PCR >3/12 UCT	PCR 3/12 NIV	PCR >3/12 NIV	First Review Results	ELISA .>=15/12 UFS	New PCR 3/12 UCT	New PCR >3/12 UCT	Final result & analysis population
184	None														
185	None														
186	04/08/98		BA Serum 18/1/99 negative	BB Serum 15/3/99 negative	BC Serum 16/8/99 negative		BA 9/11/98 Negative				Negative	BD 13/3/00 Negative			Negative PP & ITT
187	14/9/98		BA Serum 9/11/98 negative	BB Serum 22/2/99 negative	BC Serum 17/9/99 negative			BA 18/1/99 Negative			Negative	BD 3/4/00 Negative			Negative ITT
188	13/09/98		BA Serum 1/2/99 negative	BB Serum 12/4/99 negative	BC Serum 13/9/99 Negative			BA 1/2/99 Negative			Negative				Negative ITT
189	13/08/98	BA* Heparin plasma 16/11/98 positive	BA Serum 16/11/98 positive at NIV	BB Serum 01/03/99 positive	BC Serum 16/8/99 positive		BA 11/11/98 Positive		BA 11/11/98 Positive		Positive	BD 20/3/00 Positive			Positive PP & ITT
190	None														
191	13/07/98		BA Serum 4/11/98 negative	BB Serum 13/1/99 negative	BC Serum 29/9/99 negative			BB 13/1/99 Negative			Negative				Negative ITT
192	20/10/98		BA Serum 22/2/99 negative					BA 22/1/99 Negative			Negative				Negative ITT
193	None														

Pat no	DOB	P-24 1/12 UFS	P-24 3/12 UFS	P-24 6/12 UFS	P-24 12/12 UFS	P-24 >=15/12 UFS	PCR 3/12 UCT	PCR >3/12 UCT	PCR 3/12 NIV	PCR >3/12 NIV	First Review Results	ELISA .>=15/12 UFS	New PCR 3/12 UCT	New PCR >3/12 UCT	Final result & analysis population
194	21/10/98		BA Serum 18/1/99 negative				BA 18/1/99 Indeterminant Result				Re-test		BA 18/1/99 Negative		Negative PP & ITT
195	19/09/98		BA Serum 13/1/99 negative	BB Serum 17/3/99 negative	BC Serum 22/9/99 negative		BA 13/1/99 Negative				Negative	BD 3/4/00 Negative			Negative PP & ITT
196	15/10/98		BA Serum 18/10/99 negative	BB Serum 19/4/99 negative	BC Serum 18/10/99 negative		BA 18/1/99 Negative				Negative	BD 17/4/00 Negative			Negative PP & ITT
197	16/09/98			BA Serum 8/3/99 negative	BB Serum 20/9/99 negative			BA 8/3/99 Negative			Negative	BD 3/4/00 Negative			Negative ITT
198	20/08/98		BA Serum 1/3/99 negative								Re-test			BA 1/3/99 Negative	Negative ITT
199	22/09/98		BA Serum 3/2/99 positive	BB Serum 7/4/99 positive	BC Serum 6/10/99 positive			BA 3/2/99 positive			Positive	BD 17/4/00 Positive			Positive ITT
200	10/9/98		BA Serum 18/1/99 positive	BB Heparin Plasma 15/3/99 positive				BA 18/1/99 positive			Positive				Positive ITT
201	None														

Pat no	DOB	P-24 1/12 UFS	P-24 3/12 UFS	P-24 6/12 UFS	P-24 12/12 UFS	P-24 >=15/12 UFS	PCR 3/12 UCT	PCR >3/12 UCT	PCR 3/12 NIV	PCR >3/12 NIV	First Review Results	ELISA .>=15/12 UFS	New PCR 3/12 UCT	New PCR >3/12 UCT	Final result & analysis population
202	20/10/98		BA Serum 18/1/99 positive	BB Serum 26/4/99 positive	BC Serum 22/11/99 positive		BA 18/1/99 Positive				Positive				Positive PP & ITT
203	1/11/98		BA Serum 11/1/99 negative	BB Serum 27/7/99 negative	BC Heparin Plasma 11/10/99 negative		BA 11/1/99 Negative				Negative				Negative PP & ITT
204	None														
205	23/09/98		BA Serum 13/1/99 negative	BB Serum 24/3/99 negative	BC Serum 29/9/99 negative		BA 13/1/99 Negative				Negative	BE 10/4/00 Negative			Negative PP & ITT
206	18/09/98			BA Serum 8/3/99 negative							Re-test			BA 8/3/99 Negative	Negative ITT
207	21/09/98		BA Serum 6/1/99 negative	BB Serum 24/3/99 negative	BC Serum 22/9/99 negative		BA 6/1/99 Positive				Re-test	BD 10/4/00 Positive		BD 10/4/00 Positive	Positive PP & ITT
208	None														
209	None														
210	08/09/98		BA Serum 25/1/99 negative	BB Serum 29/3/99 negative	BC Serum 13/9/99 negative			BA 25/1/99 negative			Negative	BD 27/3/00 Negative			Negative ITT
211	4/9/98			BA Serum 15/3/99 negative	BB Serum 17/9/99 negative			BA 15/3/99 Negative			Negative	BC 20/3/00 Negative			Negative ITT

Pat no	DOB	P-24 1/12 UFS	P-24 3/12 UFS	P-24 6/12 UFS	P-24 12/12 UFS	P-24 >=15/12 UFS	PCR 3/12 UCT	PCR >3/12 UCT	PCR 3/12 NIV	PCR >3/12 NIV	First Review Results	ELISA .>=15/12 UFS	New PCR 3/12 UCT	New PCR >3/12 UCT	Final result & analysis population
212	None														
213	None														
214	2/11/98		BA Serum 18/1/99 negative	BB Serum 3/5/99 negative	BC Serum 8/11/99 negative		BA 18/1/99 Negative				Negative	BD 15/5/00 Negative			Negative PP & ITT
215	24/10/98		BA Serum 20/1/99 negative	BB Serum 28/4/99 negative	BC Serum 27/10/99 negative		BA 20/1/99 Negative				Negative	BD 8/5/00 Negative			Negative PP & ITT
216	None														
217	None														
218	None														
219	08/10/98		BA Serum 13/1/99 Negative		BC Serum 13/10/99 negative		BA 13/1/99 Negative				Negative	BD 8/5/00 Negative			Negative PP & ITT
220	20/09/98		BC Serum 11/1/99 negative	BB Serum 29/3/99 negative	BC Serum 20/9/99 negative						Re-test	BD 3/4/00 Negative		BB 29/3/99 Negative	Negative ITT
221	14/09/98		BA Serum 8/2/99 negative	BB Serum 14/6/99 negative	BC Serum 20/9/99 negative			BA 8/2/99 Positive			Positive	BD 3/4/00 Positive			Positive ITT
222	27/10/98		BA Serum 25/1/99 negative	BB Serum 26/4/99 negative	BC Serum 1/11/99 negative		BA 25/1/99 Negative				Negative	BD 17/4/00 Positive			Negative & Positive After 3 months PP & ITT
223	28/11/98		BA Serum 29/3/99 negative	BB Serum 7/6/99 negative	BC Serum 22/11/99 negative			BA 29/3/99 negative			Negative	BD 22/5/00 Negative			Negative ITT

Pat no	DOB	P-24 1/12 UFS	P-24 3/12 UFS	P-24 6/12 UFS	P-24 12/12 UFS	P-24 >=15/12 UFS	PCR 3/12 UCT	PCR >3/12 UCT	PCR 3/12 NIV	PCR >3/12 NIV	First Review Results	ELISA .>=15/12 UFS	New PCR 3/12 UCT	New PCR >3/12 UCT	Final result & analysis population
224	13/11/98			Baby died			BA 17/2/99 Positive				Positive				Positive PP & ITT
225	07/12/98		BA Serum 15/3/99 negative	BB Serum 7/6/99 negative	BC Serum 10/1/00 negative		BA 15/3/99 Negative				Negative	BD 12/6/00 Indeterminant Result			Negative PP & ITT
226	18/11/98	Medicine Received													
227	08/10/98			BA Serum 17/05/99 positive			BA 1/2/99 Positive				Positive				Positive PP & ITT
228	None														
229	29/11/98		BA Serum 29/3/99 negative	BB Serum 14/6/99 negative	BC Serum 17/1/00 negative			BA 29/3/99 negative			Negative				Negative ITT
230	02/12/98			BB Serum 14/6/99 negative	BC Serum 24/1/00 negative			BA 12/4/99 Negative			Negative	BD 12/6/00 Negative			Negative ITT
231	None														
232	18/10/98		BA Serum 1/3/99 negative	BB Serum 3/5/99 negative	BC Serum 25/10/99 negative			BA 1/3/99 Negative			Negative				Negative ITT
233	13/10/98							BA 1/3/99 positive			Positive				Positive ITT
234	11/01/99						BA 28/4/99 Negative				Negative	BD 26/6/00 Negative			Negative PP & ITT

Pat no	DOB	P-24 1/12 UFS	P-24 3/12 UFS	P-24 6/12 UFS	P-24 12/12 UFS	P-24 >=15/12 UFS	PCR 3/12 UCT	PCR >3/12 UCT	PCR 3/12 NIV	PCR >3/12 NIV	First Review Results	ELISA .>=15/12 UFS	New PCR 3/12 UCT	New PCR >3/12 UCT	Final result & analysis population
235	09/11/98		BA Heparin Plasma 15/3/99 negative	BB Serum 31/5/99 negative	BC Serum 8/11/99 negative			BA 15/3/99 negative			Negative	BD 15/5/00 Negative			Negative ITT
236	28/10/98		BA Serum 3/2/99 negative	BB Serum 14/4/99 negative	BC Serum 3/11/99 negative		BA 3/2/99 Negative				Negative	BD 15/5/00 Negative			Negative PP & ITT
237	None														
238	None														
239	31/10/98		BA Serum 29/3/99 negative		BC Heparin Plasma 1/11/99 negative			BA 29/3/99 Negative			Negative	BD 15/5/00 Negative			Negative ITT
240	25/11/98		BA Serum 1/3/99 positive	BB Serum 31/5/99 positive	BC Serum 22/11/99 positive		BA 1/3/99 Positive				Positive	BD 12/6/00 Positive			Positive PP & ITT
241	22/10/98		BA Serum 11/1/99 negative	BB Serum 31/5/99 negative	BC Serum 25/10/99 negative		BA 11/1/99 Negative				Negative	BC 25/10/99 Indeterminant Result			Negative PP & ITT
242	08/01/99		BA Serum 26/4/99 negative	BB Serum 12/7/99 negative	BC Serum 14/2/00 negative		BA 26/4/99 Negative				Negative	BD 26/6/00 Negative			Negative PP & ITT
243	29/03/99			BB Serum 19/7/99 negative	BC Serum 21/2/00 negative		BA 7/5/99 Negative				Negative	BD 10/7/00 Negative			Negative PP & ITT

Pat no	DOB	P-24 1/12 UFS	P-24 3/12 UFS	P-24 6/12 UFS	P-24 12/12 UFS	P-24 >=15/12 UFS	PCR 3/12 UCT	PCR >3/12 UCT	PCR 3/12 NIV	PCR >3/12 NIV	First Review Results	ELISA .>=15/12 UFS	New PCR 3/12 UCT	New PCR >3/12 UCT	Final result & analysis population
244	31/01/99		BA Serum 7/5/99 negative	BB Serum 2/8/99 negative			BA 7/5/99 Negative				Negative				Negative PP & ITT
245	None														
246	None														
247	None														
248	None														
249	None														
250	01/02/99		BA(leng) Serum 26/5/99 negative				BA 26/5/99 Negative				Negative	BC 14/8/00 Negative			Negative PP & ITT
250	01/02/99		BA(seng) Serum 26/5/99 positive				BA 26/5/99 Positive				Positive				Positive PP & ITT
251	14/01/99		BA Serum 19/4/99 negative	BB Serum 19/7/99 negative	BC Serum 21/2/00 negative		BA 19/4/99 Negative				Negative	BD 11/9/00 Negative			Negative PP & ITT
252	09/01/99		BA Serum 19/4/99 negative	BB Serum 12/7/99 negative	BC Serum 14/2/00 negative		BA 19/4/99 Negative				Negative	BD 26/1/00 Negative			Negative PP & ITT
253	15/01/99		BA Serum 21/4/99 negative		BC Serum 26/6/00 negative			BB 21/7/99 Negative			Negative	BC 26/6/00 Negative			Negative ITT

Pat no	DOB	P-24 1/12 UFS	P-24 3/12 UFS	P-24 6/12 UFS	P-24 12/12 UFS	P-24 >=15/12 UFS	PCR 3/12 UCT	PCR >3/12 UCT	PCR 3/12 NIV	PCR >3/12 NIV	First Review Results	ELISA .>=15/12 UFS	New PCR 3/12 UCT	New PCR >3/12 UCT	Final result & analysis population
254	06/01/99		BA Serum 28/4/99 negative	BB Serum 21/7/99 negative	BC Serum 21/2/00 negative		BA 28/4/99 Negative				Negative				Negative PP & ITT
255	10/02/99	Medicine Received													
256	04/03/99						BA 9/6/99 Positive				Positive				Positive PP & ITT
257	23/1/99		BA Serum 3/5/99 negative				BA 3/5/99 negative				Negative				Negative PP & ITT
258	None														
259	None														
260	12/02/99		BA Serum 17/5/99 negative	BB Serum 16/8/99 negative	BC Heparin Plasma 13/3/00 negative		BA 17/5/99 Positive				Positive	BD 14/8/00 Positive			Positive PP & ITT
261	30/01/99		BA Serum 3/5/99 negative	BB Serum 2/8/99 negative	BC Serum 6/3/99 negative		BA 3/5/99 Negative				Negative				Negative PP & ITT
262	20/02/99			BB Serum 20/9/99 negative	BC Serum 28/2/00 negative			BA 21/6/99 positive			Positive	BD 14/8/00 Positive			Positive ITT
263	04/02/99		BA Serum 5/5/99 negative	BB Serum 4/8/99 negative			BA 5/5/99 Negative				Negative				Negative PP & ITT
264	None														

Pat no	DOB	P-24 1/12 UFS	P-24 3/12 UFS	P-24 6/12 UFS	P-24 12/12 UFS	P-24 >=15/12 UFS	PCR 3/12 UCT	PCR >3/12 UCT	PCR 3/12 NIV	PCR >3/12 NIV	First Review Results	ELISA .>=15/12 UFS	New PCR 3/12 UCT	New PCR >3/12 UCT	Final result & analysis population
265	01/03/99		BA Serum 7/6/99 negative	BB Serum 6/9/99 negative	BC Serum 27/3/00 negative		BA 7/6/99 Negative				Negative	BD 11/9/00 Negative			Negative PP & ITT
266	08/03/99						BA 21/6/99 Negative				Negative	BD 11/9/00 Negative			Negative PP & ITT
267	03/02/99							BA 2/8/99 Negative			Negative				Negative ITT
268	05/02/99		BA Serum 19/5/99 positive	BB Serum 18/8/99 positive	BC Serum 6/3/00 positive		BA 19/5/99 Positive				Positive	BD 14/8/00 Positive			Positive PP & ITT
269	21/3/99		BA Serum 7/4/99 negative	BB Serum 27/9/99 negative	BC Serum 10/4/00 negative		BA 7/6/99 Negative				Negative	BD 30/10/00 Negative			Negative PP & ITT
270	None														
271	23/03/99		BA Serum 12/7/99 negative	BB Serum 11/10/99 negative	BC Serum 17/4/00 negative		BA 12/7/99 Negative				Negative	BD 30/10/00 Negative			Negative PP & ITT
272	10/03/99		BA Serum 23/6/99 negative	BB EDTA plasma 15/9/99 negative	BC Serum 27/3/00 negative		BA 23/6/99 Negative				Negative	BD 11/9/00 Negative			Negative PP & ITT
273	None														
274	17/04/99		BA Serum 19/7/99 negative	BB Serum 18/10/99 negative	BC Serum 8/5/00 negative		BA 19/7/99 Negative				Negative	BD 30/10/00 Negative			Negative PP & ITT

Pat no	DOB	P-24 1/12 UFS	P-24 3/12 UFS	P-24 6/12 UFS	P-24 12/12 UFS	P-24 >=15/12 UFS	PCR 3/12 UCT	PCR >3/12 UCT	PCR 3/12 NIV	PCR >3/12 NIV	First Review Results	ELISA .>=15/12 UFS	New PCR 3/12 UCT	New PCR >3/12 UCT	Final result & analysis population
275	13/3/99		BA EDTA Plasma 10/5/99 negative	BB Serum 16/8/99 negative	BC Serum 13/3/00 negative		BA 19/5/99 Negative				Negative	BD 11/9/00 Negative			Negative PP & ITT
276	25/03/99			BB Serum 27/9/99 negative	BC EDTA Plasma 27/3/00 negative		BA 28/6/99 Negative				Negative	BD 30/10/00 Negative			Negative PP & ITT
277	None														
278	28/03/99		BA Serum 12/7/99 positive				BA 12/7/99 Positive				Positive				Positive PP & ITT
279	21/05/99		BA Serum 6/9/99 negative	BB Serum 22/11/99 negative	BC Serum 22/5/00 negative		BA 6/9/99 Negative				Negative	BD 11/12/00 Indeterminant Result			Negative PP & ITT
280	14/02/99		BA Serum 7/6/99 negative	BB Serum 16/8/99 negative			BA 7/6/99 Negative				Negative				Negative PP & ITT
281	28/04/99	Medicine Received													
282	25/5/99			BB EDTA Plasma 22/11/99 negative			BA 16/8/99 Positive				Positive				Positive PP & ITT
283	None														
284	None														

Pat no	DOB	P-24 1/12 UFS	P-24 3/12 UFS	P-24 6/12 UFS	P-24 12/12 UFS	P-24 >=15/12 UFS	PCR 3/12 UCT	PCR >3/12 UCT	PCR 3/12 NIV	PCR >3/12 NIV	First Review Results	ELISA .>=15/12 UFS	New PCR 3/12 UCT	New PCR >3/12 UCT	Final result & analysis population
285	10/04/99		BA Serum 12/7/99 negative	BB Serum 11/10/99 negative			BA 12/7/99 Negative				Negative				Negative PP & ITT
286	None														
287	30/03/99			BB Serum 4/10/99 negative	BC Serum 17/4/00 negative		BA 5/7/99 Negative				Negative	BD 11/9/00 Negative			Negative PP & ITT
288	None														
289	23/05/99	Medicine Received													
290	13/5/99		BA Serum 2/8/99 negative	BB Serum 15/11/99 negative	BC Serum 12/6/00 negative		BA 2/8/99 Negative				Negative				Negative PP & ITT
291	08/04/99		BA Serum 12/7/99 negative	BB Serum 4/10/99 negative	BC Serum 10/4/00 negative		BA 12/7/99 Positive				Positive	BE 30/10/00 Positive			Positive PP & ITT
292	21/04/99		BA Serum 26/7/99 negative	BB Serum 1/11/99 negative	BC Serum 24/11/00 negative		BA 26/7/99 Negative				Negative	BD 30/10/00 Negative			Negative PP & ITT
293	None														
294	24/03/99		BA Serum 28/6/99 negative	BB Serum 4/10/99 negative	BC Serum 10/4/00 negative		BA 28/6/99 Negative				Negative	BD 11/9/00 Negative			Negative PP & ITT
295	26/04/99		BA Serum 30/8/99 positive	BB Serum 1/11/99 positive			BA 30/8/99 Positive				Positive				Positive PP & ITT

Pat no	DOB	P-24 1/12 UFS	P-24 3/12 UFS	P-24 6/12 UFS	P-24 12/12 UFS	P-24 >=15/12 UFS	PCR 3/12 UCT	PCR >3/12 UCT	PCR 3/12 NIV	PCR >3/12 NIV	First Review Results	ELISA .>=15/12 UFS	New PCR 3/12 UCT	New PCR >3/12 UCT	Final result & analysis population
296	None														
297	9/3/99						BA 17/5/99 Negative				Negative	BC 11/9/00 Negative			Negative PP & ITT
298	18/05/99		BA Serum 13/9/99 negative	BB Serum 17/1/00 negative	BC Serum 22/5/00 negative						Re-test	BD 11/12/00 Negative		BC 11/12/00 Negative	Negative ITT
299	None														
300	22/06/99		BA Serum 27/9/99 negative	BB EDTA plasma 31/1/00 negative	BC Serum 10/7/00 negative						Re-test			BC 10/7/00 Negative	Negative ITT
301	None														
302	None														
303	None														

CUT-OFF VALUE: FOR P-24 TESTS

08/03/99 - 0,0715
21/06/99 - 0,0745

Signatures

Vitamin A project leader
Signature: _____ Date: 22/6/2001

PRESENT:
Signature:
Professor G Joubert _____ Date 21/6/2001
Dr R Schall _____ Date 21/6/2001
Dr JI Viljoen _____ Date 22/6/2001
WJ Steinberg _____ Date 22/6/2001
Ms P Chikobvu _____ Date 22/6/2001

APPENDIX 10

Questionnaire used during patient tracing

FOLLOW-UP FORM

Background information

Woman's name .....

Woman's number .....

Address .....

.....

Date of last missed appointment ...../...../...

Antenatal/Postnatal.....

Follow-up information

Date of followup visit ...../ ...../ .....

Was the address found? YES/NO

IF ADDRESS WAS NOT FOUND

What was the problem? .....

.....

IF ADDRESS WAS FOUND

Is the woman still at this address? YES/NO

IF NO , why not?.....

.....

Source of information .....

New address if there was a change of address.....

.....

Has she delivered? YES/NO/UNKNOWN

If yes, is the baby alive? YES/NO

Was calendar collected? YES/NO

Was an appointment date made? YES/NO date...../...../.....

If no, why was no date given? .....

.....

Why did she not come for her previous appointment?.....

.....

.....

Was the woman seen at the clinic YES/NO

If the baby has died Please complete the following

When was the baby born?----------
(Give date or month)

When did the baby die?----------
(Give date or month)

Did you breast feed? YES / NO (Please circle the answer)

Also get information from the baby clinic card (if still available) for the following questions

Did you see the baby clinic card? YES / NO (Please circle the answer)

What was the cause of death----------

Was the baby Term or Prem?----------

Length of baby at birth----------

Head circumference at birth ----------

Body mass at birth ----------

APPENDIX 11

Consent forms for participating in the consent study

TOESTEMMINGSVORM

Ek wil graag 'n paar vrae vra om vas te stel hoe u sekere aspekte van die studie waarvoor u na hierdie kliniek toe kom, ervaar. As u nie die vrae wil beantwoord nie, hoef u nie. U deelname aan die studie sal nie deur u weiering beïnvloed word nie. Ons wil graag u eerlike antwoord hê en alle inligting sal streng vertroulik hanteer word. Wanneer ons verslag lewer oor die studie sal ons geen deelnemer identifiseer nie. Die resultate kan ons moontlik help om in die toekoms so 'n studie anders aan te pak.

Ek ..... stem hiermee toe om die vrae oor die studie te beantwoord.

..... geteken op .....

Getuie: .....

Kontakpersoon: Gina Joubert, Departement Biostatistiek, Tel 4013117

FOROMO YA TUMELLO

Ke tla lakatsa ho o botsa dipotso tse mmalwa ho fumana hore na o ikutlwa jwang mabapi le dintlha tse itseng tsa patlisiso eo o e tletseng mona Cliniking. Ha o sa ikemisetsa ho araba dipotso o seke wa di araba. Ho nka karolo ha hao patlisisong ha hona ho angwa ke ho se arabe ha hao. Wena le lesea la hao le tla nne le fumane tlhokomelo ya ka mehla. Re tla lakatsa ho fumana, di karabo tsa nnete ho wena, hape tsohle e tla ba sephiri. Hare tsebisa ka diphetho tsa patlisiso, hare na ho tsebisa hore na monka-korolo ke mang. Diphetho di tla re thusa ho lokisa diphapang tsa patlisiso ya mofuta ona nakong e tlang.

Nna ..... ke a dumela ho araba dipotso tsa thuto.
..... e tekennwa ka .....

Paki: .....

Mohokahanyi: Gina Joubert, Department Biostatistics, Tel 4013117

APPENDIX 12

Questionnaire for the consent study

QUESTIONNAIRE

Bakeng sa tshebediso ya kantoro

(Nomoro ya patlisiso) ☐☐☐ 1-3

Lebitso .....
Dilemo ..... ☐☐ 4-5
Sehlopha se hodimo seo o sepasitseng ..... ☐☐ 6-7
Letsatsi leo oneng o kenngwa patlisisong..... ☐☐☐☐ 8-11
(Letsatsi leo oneng o bolellwa hore ona le HIV) ☐☐☐☐☐☐ 12-17
(Letsatsi la ho kenyelletsa bopaki) ☐☐☐☐☐☐ 18-23

1. Tsebo kakaretso ka HIV

HIV ke eng ..... ☐ 24
.....

AIDS ke heng ..... ☐ 25
.....

Kokwana hloko ya HIV e ka fetisetswa ho motho emong ka mekgwa e latelang:

	Eya	Tjhe	Ha ke na bonnete	
- Ngwana ya nyanyang lebese la letswele ho mme ya nang le kokwana.....				☐ 26
- Ho kena ketsong tsa motabo le motho ya nang le kokwana ya HIV.....				☐ 27
- Moimamna ya nang le HIV a ka e fitisetsa ho lesea la hae ka nako eo le hlahang				☐ 28
- Ka ho sebedisa ntlwana e sebedisitsweng ke motho ya nang le HIV				☐ 29

Na kokwana hloko ya HIV eka thibelwa ka mekgwa e latelang:

	Eya	Tjhe	Ha ke na bonnete	
- Ho sebedisa khohlopo (condom) ka nako ya thobalano				☐ 30
- Ka ho etsa thobalano le molekane a le mong feela				☐ 31
- Ho ja dijo tse bolokehileng tsa bohlokwa				☐ 32
-Ho nwa meriana				☐ 33
-Ka ho etsa operation				☐ 34
Na kokwana hloko ya HIV e ka o bolaya				☐ 35
Na kokwana hloko ya HIV e ya phekola				☐ 36

Na HIV ke lefu le tshwaetsang? ☐ 37

2. Maikutlo ka motho ya nang le HIV

Eya Tjhe Ha ke na bonnete

- Na lesea le ka fumana HIV ho mma ona.ka nako ya boimane? ☐ 38
- Na kokwana hloko ya HIV e ka eketseha kapa ya tota ha motho e le moimana? ☐ 39

3. Lesedi kapa tlhakisetso eo o e fumaneng

Eya Tjhe Ha ke na bonnete

- Na o fumane tlhakisetso pele o etswa diteko tsa HIV? ☐ 40
- Ebang o e fumana: ☐ 41
  - Na io ile wa e utlwisisa?
  - Na o nahana hore o tseba ho lekaneng ka HIV? ☐ 42

Na o sa na le dipotse mabapi le HIV? ☐ 43

Ebang di leng teng, ke dife? .....

.....

44-45 ☐☐

4. Lesedi kapa tlhalosetso mabapi le dipatlisiso

K emoriana ofe o sebediswang patlisisong? ..... ☐ 46

.....

O fellwa eng moriana ona? ..... ☐ 47

.....

O lokela ho nwa dipidisi tse kae ka letsatsi pele ngwana a hlaha? ☐ 48

.....

O lokela ho ya kliniking ka makgetlo a makae?

Pele o pepa? ..... ☐ 49

Ha ose o pepile? ..... ☐ 50

O tla tseba neng ebang ngwana le yena o fumane kokwana hloko ya HIV?

.....

O tshwanela ho etela tliniki ho fihlela neng bakeng sa patlisiso ena?

..... ☐ 51

5. Maikutlo mabapi le tlhalosetso ya tumello ya ho nka madi

	Eya	Tjhe	Ha ke na bonnete	
- Na o dumetse hore o hlahlojwe HIV?				☐ 52
- O dumetse hoba karolo ya patlisiso?				☐ 53
- Na o qobelletswe ho nka karole patlisisong ena?				☐ 54
- Na o ka emisa nako enngwe le enngwe ho ba karolo ya patlisiso ena?				☐ 55
- Na o ile wa dumellwa ho botsa dipotso ka nako eo o neng o dumela ho nka karolo patlisisong?				☐ 56
- O nahana hore ha o ka emisa ka ho nka karolo mona patlisisong ha o satla fumana tlhokomelo e ntle ya booki?				☐ 57

VRAELYSTE:

Kantoorgebruik

oefnommer.....

Naam.....
Ouderdom.....
Hoogste standerd geslaag.....
. Datum van HIV positiewe diagnose.....
. Datum van insluiting in proef.....
. Datum van onderhoud.....

. Algemene kennis rakende HIV

> Wat is HIV ?

> Wat is VIGS ?

> Kan HIV oorgedra word deur :

Ja	Nee	Onseker

~ 'n baba wat aan HIV positiewe ma drink
~ seksuele omgang met iemand wat HIV positief is
~ 'n HIV positiewe ma aan haar baba tydens geboorte
~ op 'n toilet sitplek te sit wat voorheen deur 'n HIV positiewe persoon gebruik is

> Kan HIV op die volgende manier voorkom word ?

~ deur kondome te gebruik tydens seksuele omgang
~ deur seksuele omgang met slegs een maat te hê
~ gesonde kos te eet
~ deur medisyne te drink
~ deur 'n operasie te ondergaan

> Kan HIV u doodmaak ?

> Kan HIV gesond gemaak word ?

> Is HIV 'n aansteeklike siekte ?

	Ja	Nee	Onseker	Kantoorgebruik

2. Aspekte rakende 'n HIV positiewe swanger vrou

- kan die baba HIV van die moeder kry gedurende swangerskap ?
- kan HIV erger word terwyl die vrou swanger is ?

3. Voorligting aan u gegee

- Is daar voorligting vir u gegee voor die HIV toets ?
- Indien ja :
  - ~ het u die voorligting verstaan ?
  - ~ voel u u weet nou genoeg van HIV ?
- Het u nog vrae oor HIV ? Indien wel, wat ?

Kantoorgebruik

. Inligting rakende die proef

Watter medisyne word in die proef gebruik ? ☐

Waarvoor word die medisyne gegee ? ☐

Hoeveel pille moet u per dag drink in die tyd voor die baba se geboorte ? ☐

Hoe gereeld moet u die kliniek bywoon

~ voor kraam ? ☐

~ na kraam ? ☐

Wanneer sal u weet of die baba HIV positief is ? ☐

Tot wanneer moet u kliniek toe kom vir die proef ? ☐

	Ja	Nee	Onseker	Kantoorgebruik
5. Persepsies rakende ingeligte toestemming				
> Het u ingestem dat hulle u toets vir HIV ?				
> Wou u deelneem aan die proef ?				
> Het u verplig gevoel om deel te neem aan die proef ?				
> Kan u enige tyd met die proef ophou ?				
> Was u toegelaat om vrae te vra toe u besluit het om deel te neem aan die proef ?				
> Voel u dat as u ophou met die proef u nie meer goeie mediese sorg sal kry nie ?				

APPENDIX 13

Last visit attended, reason for withdrawal and further description by treatment

Population: All randomised

Treatment	Patient number	Last visit attended	Reasons for Withdrawal	Further description
	2	Post-delivery 18 months	N/A	
Vitamin A	3	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
	5	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
	8	Post-delivery 15 months	Non-compliance	Patient attended one postnatal visit only
	12	Post -delivery 3 months	Lost to follow-up	Patient attended only two postnatal visits
	13	Post-delivery 18 months	N/A	
	14	Post delivery 15 months	Lost to follow-up	
	16	Pre-delivery visit 2	Baby died	Patient reported to the sister at the clinic
	18	Post-delivery 18 months	N/A	
	20	Post-delivery 15 months	Lost to follow-up	
	22	Post-delivery 15 months	Non-compliance	Patient attended one postnatal visit only
	23	Pre-delivery visit 2	Lost to follow-up	Patient never attended any postnatal visit
	25	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
	29	Pre-delivery visit 2	Lost to follow-up	Patient never attended any postnatal visit
	30	Pre-delivery visit 3	Lost to follow-up	Patient never attended any postnatal visit
	32	Pre-delivery visit 3	Lost to follow-up	Patient never attended any postnatal visit
	33	Pre-delivery visit 2	Lost to follow-up	Patient never attended any postnatal visit
	35	Post-delivery 6 months	Lost to follow-up	Patient attend only two postnatal visits
	37	Post-delivery 6 months	Lost to Follow-up	
	38	Post-delivery 15 months	Lost to follow-up	
	41	Pre-delivery visit 2	Lost to follow-up	Patient never attended any postnatal visit
	45	Post delivery 18 months	N/A	
	46	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
	47	Pre-delivery visit 2	Lost to follow-up	Patient never attended any postnatal visit
	50	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
	51	Pre-delivery visit 2	Lost to follow-up	Patient never attended any postnatal visit
	52	Post- delivery 18 months	N/A	
	53	Post-delivery 1 month	Consent withdrawn	Information obtained by hospice people
	58	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
	62	Pre-delivery visit 2	Lost to follow-up	Patient never attended any postnatal visit
	63	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
	64	Post-delivery 18 months	N/A	
	69	Post-delivery 18 months	N/A	
	70	Pre-delivery visit 2	Lost to follow-up	Patient never attended any postnatal visit
	71	Pre-delivery visit 3	Consent withdrawn	Information obtained by hospice people
	72	Post-delivery 1 month	Lost to follow-up	Patient attended one postnatal visit only
	73	Pre-delivery visit 2	Baby died	Information obtained by hospice people
	76	Post-delivery 1 month	Baby died	Mother reported to the doctor
	79	Post-delivery 9 months	Lost to follow-up	
	80	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
	84	Post-delivery 18 months	N/A	
	85	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
	87	Post-delivery 18 months	N/A	
	88	Post-delivery 15 months	Non-compliance	Patient attended one postnatal visit only
	89	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
	92	Post-delivery 1 month	Lost to follow-up	Patient attended one postnatal visit only
	93	Pre-delivery visit 2	Consent withdrawn	Information obtained by Hospice people
	94	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
	99	Post-delivery 9 months	Lost to follow-up	
	100	Post-delivery 9 months	Non-compliance	Patient attended one postnatal visit only
	101	Pre-delivery visit 1	Consent withdrawn	Information obtained by hospice people
	102	Pre-delivery visit 2	Lost to follow-up	Patient never attended any postnatal visit
	105	Pre-delivery visit 3	Lost to follow-up	Patient never attended any postnatal visit
	106	Post-delivery 3 months	Baby died	Patient reported to the doctor & hospice
	110	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
	111	Post-delivery 9 months	Non-compliance	Patient attended one postnatal visit only
	115	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
	116	Post-delivery 18 months	N/A	
	117	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
	119	Pre- delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
	121	Post-delivery 12 months	Lost to follow-up	
	123	Post-delivery 18 months	N/A	
	125	Post-delivery 18 months	N/A	
	127	Pre-delivery visit 2	Lost to follow-up	Patient never attended any postnatal visit
	131	Pre-delivery visit 2	Lost to follow-up	Patient never attended any postnatal visit

132	Pre-delivery visit 2	Lost to follow-up	Patient never attended any postnatal visit
133	Pre- delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
136	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
138	Post-delivery 18 months	N/A	
142	Post- delivery 12 months	Non-compliance	Patient attended one postnatal visit only
143	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
144	Post-delivery 9 months	Lost to follow-up	
145	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
148	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
149	Post-delivery 18 months	N/A	
150	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
154	Post-delivery 18 months	N/A	
155	Post-delivery 18 months	N/A	
158	Pre-delivery visit1	Lost to follow-up	Patient never attended any postnatal visit
159	Post-delivery 18 months	N/A	
162	Post-delivery 3 months	Lost to follow-up	Patient attended one postnatal visit only
163	Pre-delivery visit 1	Baby died	Patient reported to the study monitor
166	Post-delivery 18 months	N/A	
168	Pre-delivery visit 2	Lost to follow-up	Patient never attended any postnatal visit
169	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
170	Pre-delivery visit 1	Consent withdrawn	Information obtained by hospice people
175	Post delivery 15 months	Lost to follow-up	
176	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
177	Pre-delivery visit 2	Lost to follow-up	Patient never attended any postnatal visit
179	Post-delivery 18 months	N/A	
183	Pre-delivery visit 1	Consent withdrawn	Information obtained by hospice people
184	Pre-delivery visit 2	Lost to follow-up	Patient never attended any postnatal visit
186	Post-delivery 18 months	N/A	
188	Post-delivery 12 months	Lost to follow-up	
189	Post delivery 18 months	N/A	
192	Post-delivery 3 months	Lost to follow-up	Patient attended one postnatal visit only
194	Post-delivery 3 months	Lost to follow-up	Patient attended two postnatal visits only
195	Post-delivery 18 months	N/A	
196	Post-delivery 18 months	N/A	
198	Post-delivery 6 months	Non-compliance	Patient attended one postnatal visit
203	Post-delivery 15 months	Lost to follow-up	
205	Post-delivery 18 months	N/A	
206	Post-delivery 6 months	Lost to follow-up	Patient attended one postnatal visit only
208	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
209	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
210	Post-delivery 18 months	N/A	
211	Post-delivery 18 months	N/A	
212	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
217	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
221	Post-delivery 18 months	N/A	
223	Post-delivery 18 months	N/A	
224	Post-delivery 3 months	Baby died	Patient reported to study monitor
225	Post-delivery 18 months	N/A	
226	Post-delivery 1 month	Baby died	Patient reported to the doctor
228	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
231	Pre-delivery visit 2	Baby died	Information obtained by hospice people
233	Post-delivery 3 months	Lost to follow-up	Patient attended one postnatal visit only
235	Post-delivery 18 months	N/A	
238	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
240	Post delivery 18 months	N/A	
243	Post-delivery 18 months	N/A	
244	Post-delivery 6 months	Lost to follow-up	
245	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
248	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
250	Post-delivery 18 months	N/A	
151	Post delivery 18 months	N/A	
254	Post delivery 18 months	N/A	
255	Post-delivery 3 months	Baby died	Patient reported to the doctor
260	Post-delivery 18 months	N/A	
261	Post-delivery 12 months	Lost to follow-up	
263	Post-delivery 6 months	Lost to follow-up	
264	Pre-delivery visit 2	Lost to follow-up	Patient never attended any postnatal visit
265	Post-delivery 18 months	N/A	
268	Post-delivery 18 months	N/A	
270	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit

	272	Post -delivery 18 months	N/A	
	273	Pre-delivery visit 2	Lost to follow-up	Patient never attended any postnatal visit
	277	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
	278	Post-delivery 3 months	Lost to follow-up	Patient attended two postnatal visit only
	280	Post-delivery 9 months	Lost to follow-up	
	285	Post-delivery 6 months	Lost to follow-up	Patient attended two postnatal visits only
	286	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
	287	Post-delivery 18 months	N/A	
	288	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
	292	Post-delivery 18 months	N/A	
	293	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
	294	Post delivery 18 months	N/A	
	296	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
	299	Pre-delivery visit 2	Lost to follow-up	Patient never attended any postnatal visit
	300	Post-delivery 15 months	Lost to follow-up	
	301	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
	303	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
	1	Pre-delivery visit 1	In utero death	Patient reported to the doctor
Placebo	4	Pre-delivery visit 2	Lost to follow-up	Patient never attended any postnatal visit
	6	Post-delivery 15 months	Non-compliance	Patient attended one postnatal visit only
	7	Post delivery 15 months	Lost to follow-up	
	9	Post delivery 6 months	Baby died	Patient reported to the doctor
	10	Post-delivery 9 months	Lost to follow-up	
	11	Post-delivery 15 months	Lost to follow-up	
	15	Post-delivery 18 months	N/A	
	17	Post-delivery 18 months	N/A	
	19	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
	21	Pre-delivery visit 2	Lost to follow-up	Patient never attended any postnatal visit
	24	Pre-delivery visit 2	Lost to follow-up	Patient never attended any postnatal visit
	26	Pre-delivery visit 2	Lost to follow-up	Patient never attended any postnatal visit
	27	Post-delivery 6 months	Baby died	Patient reported to the doctor
	28	Post delivery 3 months	Baby died	Patent reported to counselor at the clinic
	31	Pre-delivery visit 2	Baby died	Information obtained by hospice people
	34	Post-delivery 18 months	N/A	
	36	Post-delivery 18 months	N/A	
	39	Post-delivery 18 months	N/A	
	40	Post delivery 1 month	Baby died	Patient reported to the doctor
	42	Pr-delivery visit 2	Lost to follow-up	Patient never attended any postnatal visit
	43	Pre-delivery visit 2	Lost to follow-up	Patient never attended any postnatal visit
	44	Post-delivery 18 months	N/A	
	48	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
	49	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
	54	Post-delivery 12 months	Lost to follow-up	
	55	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
	56	Post-delivery 6 months	Lost to follow-up	
	57	Post-delivery 12 months	Non-compliance	Patient attended two postnatal visit only
	59	Post-delivery 15 months	Non-compliance	Patient attended one postnatal visit only
	60	Post-delivery 18 months	N/A	
	61	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
	65	Post-delivery 18 months	N/A	
	66	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
	67	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
	68	Post-delivery 18 months	N/A	
	74	Pre-delivery visit 1	Consent withdrawn	Information obtained by hospice people
	75	Post-delivery 18 months	N/A	
	77	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
	78	Post-delivery 12 months	non-compliance	Patient attended one postnatal visit only
	81	Pre-delivery visit 2	Lost to follow-up	Patient never attended any postnatal visit
	82	Post-delivery 18 months	N/A	
	83	Pre-delivery visit 1	Baby died	Information obtained by hospice people
	86	Post-delivery 18 months	N/A	
	90	Post-delivery 18 months	N/A	
	91	Post-delivery 9 months	Lost to follow-up	
	95	Post-delivery 1 month	Consent withdrawn	Information obtained by hospice people
	96	Pre-delivery visit 2	Lost to follow-up	Patient never attended any postnatal visit
	97	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
	98	Post-delivery 18 months	N/A	
	103	Post-delivery 18 months	N/A	

104	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
107	Post-delivery 3 months	Baby died	Patient reported to the doctor & hospice
108	Pre-delivery visit 2	Baby died	Information obtained by hospice people
109	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
112	Post-delivery 1 month	Baby died	Patient reported to the doctor
113	Post-delivery 12 months	Non-compliance	Patient attended one postnatal visit only
114	Post-delivery 18 months	N/A	
118	Pre-delivery visit 2	Lost to follow-up	Patient never attended any postnatal visit
120	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
122	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
124	Pre-delivery visit 3	Baby died	Information obtained by hospice people
126	Post-delivery 6 months	Lost to follow-up	
128	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
129	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
130	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
134	Pre-delivery visit 2	Lost to follow-up	Patient never attended any postnatal visit
135	Post-delivery 9 months	Lost to follow-up	
137	Pre-delivery visit 2	Lost to follow-up	Patient never attended any postnatal visit
139	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
140	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
141	Post-delivery 18 months	N/A	
146	Post-delivery 18 months	N/A	
147	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
151	Post-delivery 9 months	Non-compliance	Patient attended one postnatal visit only
152	Pre-delivery visit 3	Lost to follow-up	Patient never attended any postnatal visit
153	Post-delivery 12 months	Lost to follow-up	
156	Post-delivery 9 months	Non-compliance	Patient attended one postnatal visit only
157	Post-delivery 18 months	N/A	
160	Post-delivery 3 months	Lost to follow-up	Patient attended one postnatal visit only
161	Post-delivery 18 months	N/A	
164	Pre-delivery visit 2	Lost to follow-up	Patient never attended any postnatal visit
165	Post-delivery 1 month	Baby died	Information obtained by hospice people
167	Pre-delivery visit 2	Patient died	Information obtained by hospice people
171	Post-delivery 18 months	N/A	
172	Post-delivery 1 month	Lost to follow-up	Patient attended one postnatal visit only
173	Pre-delivery visit 2	Lost to follow-up	Patient never attended any postnatal visit
174	Post-delivery 18 months	N/A	
178	Post-delivery 18 months	N/A	
180	Pre-delivery visit 3	Lost to follow-up	Patient never attended any postnatal visit
181	Pre-delivery visit 2	Baby died	Information obtained by hospice people
182	Post-delivery 3 months	Consent withdrawn	Patient reported to doctor &study monitor
185	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
187	Post-delivery 18 months	N/A	
190	Post-delivery 1 month	Baby died	Patient reported to the doctor
191	Post-delivery 12 months	Lost to follow-up	
193	Pre-delivery visit 1	Consent withdrawn	Information obtained by hospice people
197	Post-delivery 18 months	N/A	
199	Post-delivery 18 months	N/A	
200	Post-delivery 6 months	Baby died	Information obtained by hospice people
201	Pre-delivery visit 2	Lost to follow-up	Patient never attended any postnatal visit
202	Post-delivery 15 months	Lost to follow-up	
204	Pre-delivery visit 3	Lost to follow-up	Patient never attended any postnatal visit
207	Post-delivery 18 months	N/A	
213	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
214	Post-delivery 18 months	N/A	
215	Post-delivery 18 months	N/A	
216	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
218	Pre-delivery visit 2	Lost to follow-up	Patient never attended any postnatal visit
219	Post-delivery 18 months	N/A	
220	Post-delivery 18 months	N/A	
222	Post-delivery18 months	N/A	
227	Post-delivery 9 months	Consent withdrawn	Patient reported to the doctor
229	Post-delivery 15 months	Lost to follow-up	
230	Post-delivery 18 months	N/A	
232	Post-delivery 15 months	Lost to follow-up	
234	Post-delivery 18 months	N/A	
236	Post-delivery 18 months	N/A	
237	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
239	Post-delivery 18 months	N/A	
241	Post-delivery 15 months	Lost to follow-up	

242	Post-delivery 18 months	N/A	
246	Pre-delivery visit 2	Consent withdrawn	Information obtained by hospice people
247	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
249	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
252	Post-delivery 18 months	N/A	
253	Post-delivery 18 months	N/A	
256	Post-delivery 3 months	Baby died	Patient reported to the doctor
257	Post-delivery 3 months	Lost to follow-up	
258	Post-delivery 9 months	Non-compliance	Patient attended one postnatal visit only
259	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
262	Post-delivery 18 months	N/A	
266	Post-delivery 18 months	N/A	
267	Post-delivery 12 months	Lost to follow-up	
269	Post-delivery 18 months	N/A	
271	Post-delivery 18 months	N/A	
274	Post-delivery 18 months	N/A	
275	Post-delivery 18 months	N/A	
276	Post-delivery 18 months	N/A	
279	Post-delivery 18 months	N/A	
281	Post-delivery 6 months	Baby died	Patient reported to the doctor & hospice
282	Post-delivery 6 months	Lost to follow-up	Patient attended two postnatal visits only
283	Pre-delivery visit 1	Lost to, follow-up	Patient never attended any postnatal visit
284	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit
289	Post-delivery 1 month	Lost to follow-up	Patient attended one postnatal visit only
290	Post-delivery 15 months	Lost to follow-up	
291	Post-delivery 18 months	N/A	
295	Post-delivery 6 months	Lost to follow-up	
297	Post-delivery 15 months	Lost to follow-up	
298	Post-delivery 18 months	N/A	
302	Pre-delivery visit 1	Lost to follow-up	Patient never attended any postnatal visit

APPENDIX 14

Last visit attended, reason for exclusion from efficacy analysis and protocol violations

Population: Not in ITT and not in PP

Treatment	Patient number	Last visit attended	Reasons for exclusion from ITT and PP populations	Protocol violations
Vitamin A	3	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
	5	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
	8	Post-delivery 15 months	Conflicting infant HIV result	PCR positive ELISA negative from same sample
	16	Pre-delivery visit 2	No infant HIV result	Baby died before blood was drawn
	23	Pre-delivery visit 2	No infant HIV result	Patient never attended any postnatal visit
	25	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
	29	Pre-delivery visit 2	No infant HIV result	Patient never attended any postnatal visit
	30	Pre-delivery visit 3	No infant HIV result	Patient never attended any postnatal visit
	32	Pre-delivery visit 3	No infant HIV result	Patient never attended any postnatal visit
	33	Pre-delivery visit 2	No infant HIV result	Patient never attended any postnatal visit
	37	Post-delivery 6 months	No infant HIV result	No blood was drawn from the baby
	41	Pre-delivery visit 2	No infant HIV result	Patient never attended any postnatal visit
	46	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
	47	Pre-delivery visit 2	No infant HIV result	Patient never attended any postnatal visit
	50	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
	51	Pre-delivery visit 2	No infant HIV result	Patient never attended any postnatal visit
	53	Post-delivery 1 month	No infant HIV result	Patient attended one postnatal visit only
	58	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
	62	Pre-delivery visit 2	No infant HIV result	Patient never attended any postnatal visit
	63	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
	70	Pre-delivery visit 2	No infant HIV result	Patient never attended any postnatal visit
	71	Pre-delivery visit 3	No infant HIV result	Patient never attended any postnatal visit
	72	Post-delivery 1 month	No infant HIV result	Patient attended one postnatal visit only
	73	Pre-delivery visit 2	No infant HIV result	Baby died before blood was drawn
	76	Post-delivery 1 month	No infant HIV result	Baby died before blood was drawn
	80	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
	85	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
	89	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
	92	Post-delivery 1 month	No infant HIV result	Patient attended one postnatal visit only
	93	Pre-delivery visit 2	No infant HIV result	Patient never attended any postnatal visit
	94	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
	101	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
	102	Pre-delivery visit 2	No infant HIV result	Patient never attended any postnatal visit
	105	Pre-delivery visit 3	No infant HIV result	Patient never attended any postnatal visit
	110	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
	115	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
	117	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
	119	Pre- delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
	127	Pre-delivery visit 2	No infant HIV result	Patient never attended any postnatal visit
	131	Pre-delivery visit 2	No infant HIV result	Patient never attended any postnatal visit
	132	Pre-delivery visit 2	No infant HIV result	Patient never attended any postnatal visit
	133	Pre- delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
	136	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
	143	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
	145	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
	148	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
	150	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
	158	Pre-delivery visit1	No infant HIV result	Patient never attended any postnatal visit
	163	Pre-delivery visit 1	No infant HIV result	Baby died before blood is drawn
	168	Pre-delivery visit 2	No infant HIV result	Patient never attended any postnatal visit
	169	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
	170	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
	176	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
	177	Pre-delivery visit 2	No infant HIV result	Patient never attended any postnatal visit
	183	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
	184	Pre-delivery visit 2	No infant HIV result	Patient never attended any postnatal visit
	208	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
	209	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
	212	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
	217	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
	226	Post-delivery 1 month	No infant HIV result	Baby died before blood is drawn
	228	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
	231	Pre-delivery visit 2	No infant HIV result	Baby died before blood is drawn
	238	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit

	245	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
	248	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
	250	Post-delivery 18 months	Conflicting twins HIV results	Twins one negative the other positive
	255	Post-delivery 3 months	No infant HIV result	Baby died before blood is drawn
	264	Pre-delivery visit 2	No infant HIV result	Patient never attended any postnatal visit
	270	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
	273	Pre-delivery visit 2	No infant HIV result	Patient never attended any postnatal visit
	277	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
	286	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
	288	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
	293	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
	296	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
	299	Pre-delivery visit 2	No infant HIV result	Patient never attended any postnatal visit
	301	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
	303	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
	1	Pre-delivery visit 1	No infant HIV result	Baby died before blood is drawn
Placebo	4	Pre-delivery visit 2	No infant HIV result	Patient never attended any postnatal visit
	19	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
	21	Pre-delivery visit 2	No infant HIV result	Patient never attended any postnatal visit
	24	Pre-delivery visit 2	No infant HIV result	Patient never attended any postnatal visit
	26	Pre-delivery visit 2	No infant HIV result	Patient never attended any postnatal visit
	31	Pre-delivery visit 2	No infant HIV result	Baby died before blood is drawn
	40	Post delivery 1 month	No infant HIV result	Baby died before blood is drawn
	42	Pr-delivery visit 2	No infant HIV result	Patient never attended any postnatal visit
	43	Pre-delivery visit 2	No infant HIV result	Patient never attended any postnatal visit
	48	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
	49	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
	55	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
	61	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
	66	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
	67	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
	74	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
	77	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
	81	Pre-delivery visit 2	No infant HIV result	Patient never attended any postnatal visit
	83	Pre-delivery visit 1	No infant HIV result	Baby died before blood is drawn
	95	Post-delivery 1 month	No infant HIV result	Patient attended one postnatal visit only
	96	Pre-delivery visit 2	No infant HIV result	Patient never attended any postnatal visit
	97	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
	104	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
	108	Pre-delivery visit 2	No infant HIV result	Baby died before blood is drawn
	109	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
	112	Post-delivery 1 month	No infant HIV result	Baby died before blood is drawn
	118	Pre-delivery visit 2	No infant HIV result	Patient never attended any postnatal visit
	120	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
	122	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
	124	Pre-delivery visit 3	No infant HIV result	Baby died before blood is drawn
	128	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
	129	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
	130	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
	134	Pre-delivery visit 2	No infant HIV result	Patient never attended any postnatal visit
	137	Pre-delivery visit 2	No infant HIV result	Patient never attended any postnatal visit
	139	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
	140	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
	147	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
	152	Pre-delivery visit 3	No infant HIV result	Patient never attended any postnatal visit
	164	Pre-delivery visit 2	No infant HIV result	Patient never attended any postnatal visit
	165	Post-delivery 1 month	No infant HIV result	Baby died before blood is drawn
	167	Pre-delivery visit 2	No infant HIV result	Patient died
	172	Post-delivery 1 month	No infant HIV result	Patient attended one postnatal visit only
	173	Pre-delivery visit 2	No infant HIV result	Patient never attended any postnatal visit
	180	Pre-delivery visit 3	No infant HIV result	Patient never attended any postnatal visit
	181	Pre-delivery visit 2	No infant HIV result	Baby died before blood is drawn
	185	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
	190	Post-delivery 1 month	No infant HIV result	Baby died before blood is drawn
	193	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
	201	Pre-delivery visit 2	No infant HIV result	Patient never attended any postnatal visit
	204	Pre-delivery visit 3	No infant HIV result	Patient never attended any postnatal visit
	213	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit

216	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
218	Pre-delivery visit 2	No infant HIV result	Patient never attended any postnatal visit
237	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
246	Pre-delivery visit 2	No infant HIV result	Patient never attended any postnatal visit
247	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
249	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
258	Post-delivery 9 months	No infant HIV result	Patient attended one postnatal visit only
259	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
281	Post-delivery 6 months	No infant HIV result	Baby died before blood is drawn
283	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
284	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit
289	Post-delivery 1 month	No infant HIV result	Patient attended one postnatal visit only
302	Pre-delivery visit 1	No infant HIV result	Patient never attended any postnatal visit

APPENDIX 15

The patients who brought back their diaries and the time they took the tablets

Patient number	1997Period tablets taken	1998 Period tablets taken	1999 Period tablets taken
5	18 Sept -to- 11 Nov		
8	25 Sept -to -31 Dec		
11	2 October- to -	31 Jan	
18	9 Oct -to -31 Dec		
24	1 Oct-to-20 Oct.	Patient claims she took tablets up to delivery	but did not mark the diary
30	23 Oct-to-27 Dec	8 Jan-to-28Feb	
31	23 Oct –to- 24 Dec		
35	30 Oct –to-	12 Feb	
38	7 Nov –to-	5 Jan	
39	12 Nov –to-	13 Jan	
42	20 Nov -to	15 Jan	
43	20 Nov-to-	15 Jan	
44	21 Nov –to-	16 Jan	
47	27 Nov –to-	22 Jan	
51	28 Nov –to-	25 Jan	
52	28 Nov –to-	4 Feb	
56	4 Dec –to-	23 Feb	
59	4,5,6, 8,10 & 11 Dec	8Jan -to- Feb	
62	5 Dec –to-	31 Jan	
65	11 Dec –to-	12 April	
68	12 Dec –to-	19 May	
70		8 Jan –to- 28 Feb	
72		8 Jan –to-28 Feb	
75		8 Jan-to-4 Mar; 13 Mar –to-17 April	
76		16, 18, 20, 23 Jan	
84		22 Jan –to-21 May	
86		29 Jan –to-26 Mar	
92		13 Feb-to-30 April	
98		20 Feb-to-22 Mar; 26 Mar-to-16 April	
99		20Feb-to 20April	
102		26 Feb –to-29 Mar; 1 April-to-30April	
108		5 Mar –to-30 April	
112		13 Mar; 15May-to-27July. Patient claims she	took tablets from 13 Mar to 14 May without marking diary
116		19 Mar-to-31May	
125		27 Mar-to-7July	
126		2 April –to-24 July	
131		9 April –to-31 May	
135		15 April -to- 8July	
146		Calendar spoilt	
149		7May –to-30 Sept	
157		11 May-to-11 Aug	
166		22 May-to-31 Aug	
171		4 Jun –to-31 Aug	
175		11 Jun-to-24Jun; 27Jun-to-31 Aug	
178		11th and 13th June	
188		19 Jun-to-22 Sept	
203		23, 29 and 30th July	
206		24 July –to-18 Sept	
221		14 Aug –to- 10 Sept	
224		21 Aug -to-31 Oct	
225		21 Aug-to-31Oct	
229		3 Sept-to-29 Nov	
236		11 Sept-to-27Oct	
238		6 Sept-to-8 Nov	
240		17 Sept-to-25 Nov	
243		8Oct-to-	11 Jan
260		12 Nov-to-	11Feb
267		26 Nov-to-	24 Jan
269			7 Jan-to-28 Feb
272			11 Jan –to-10 Mar
275			21J an-to-13Mar; 22, 24,25and26 Mar; 8Apr-to-11Apr
276			22Jan –to-22 Mar
294			18Feb-to-8 April
295			18Feb-to-26 April
298			25 Feb-to-17 May

APPENDIX 16

HIV symptoms on medical history for all the mothers in Safety population who attended the visit

	Variable	Vitamin A N=58		Placebo N=56		P-value
		n	%	n	%	
Post-delivery 1 month	Night sweats	0	0.0	0	0.0	
					N=55	
	Coughing	1	1.7	0	0.0	0.3280
	Fever	1	1.7	0	0.0	0.3237
	Nausea/Vomiting	0	0.0	0	0.0	
	Headache	5	8.6	3	5.5	0.4953
	Confusion		N=57		N=54	
		1	1.8	0	0.0	0.3282
			N=67		N=74	
Post-delivery 3 months	Night sweats	2	3.0	1	1.2	0.5020
	Coughing	1	1.5	3	4.1	0.3602
	Fever	2	3.0	0	0.0	0.1344
	Nausea/Vomiting	0	0.0	0	0.0	
	Headache	2	3.0	4	5.4	0.4771
	Confusion	0	0.0	0	0.0	
			N=57		N=70	
Post-delivery 6 months	Night sweats	2	3.5	0	0.0	0.1142
	Coughing	2	3.5	2	2.9	0.8344
	Fever	0	0.0	1	1.4	0.3650
	Nausea/Vomiting	0	0.0	0	0.0	
	Headache	1	1.8	3	4.3	0.4166
	Confusion	0	0.0	0	0.0	
			N=55		N=63	
Post-delivery 9 months	Night sweats	1	1.8	0	0.0	0.2825
	Coughing	3	5.5	1	1.6	0.2469
	Fever	2	3.6	2	3.2	0.8900
	Nausea/Vomiting	0	0.0	0	0.0	
	Headache	4	7.3	4	6.3	0.8422
	Confusion	0	0.0	2	3.2	0.1866
			N=50		N=60	
Post-delivery 12 months	Night sweats	0	0.0	0	0.0	
	Coughing	2	4.0	0	0.0	0.1179
	Fever	1	2.0	0	0.0	0.2711
	Nausea/Vomiting	0	0.0	0	0.0	
	Headache	4	8.0	2	3.3	0.2832
	Confusion	0	0.0	1	1.7	0.3639
			N=49		N=54	
Post-delivery 15 months	Night sweats	0	0.0	0	0.0	
	Coughing	0	0.0	1	1.9	0.3384
	Fever	0	0.0	1	1.9	0.3384
	Nausea/Vomiting	0	0.0	0	0.0	
	Headache	0	0.0	2	3.7	0.1737
	Confusion	0	0.0	0	0.0	

			N=42		N=49	
Post-delivery 18 months	Night sweats	0	0.0	0	0.0	
	Coughing	1	2.4	5	10.2	0.1338
	Fever	0	0.0	0	0.0	
	Nausea/Vomiting	0	0.0	0	0.0	
	Headache	3	7.1	3	6.1	0.8450
	Confusion	0	0.0	0	0.0	

APPENDIX 17

HIV symptoms on medical history for all the infants in Safety population who attended the visit

Visit		Vitamin A N=58		Placebo N=56		P-value
		n	%	N	%	
Post-delivery1 months	Night sweats	0	0.0	0	0.0	
	Coughing	2	3.5	4	7.1	0.3772
	Fever	2	3.5	2	3.6	0.9715
	Nausea/Vomiting	2	3.5	1	1.8	0.5793
			N=67		N=74	
Post-delivery 3 months	Night sweats	3	4.5	0	0.0	0.0658
	Coughing	7	10.5	6	8.1	0.6315
	Fever	3	4.5	2	2.7	0.5693
	Nausea/Vomiting				N=73	
		2	3.0	1	1.4	0.5097
			N=59		N=69	
Post-delivery 6months	Night sweats	1	1.7	0	0.0	0.2776
	Coughing	9	15.3	9	13.0	0.7199
	Fever	3	5.1	6	8.7	0.4258
	Nausea/Vomiting	2	3.4	2	2.9	0.8735
			N=56		N=64	
Post-delivery 9 months	Night sweats	1	1.8	2	3.1	0.6392
	Coughing	12	21.4	10	15.6	0.4124
	Fever	4	7.1	4	6.3	0.8449
	Nausea/Vomiting		N=53			
		2	3.8	2	3.1	0.8476
			N=49		N=58	
Post-delivery 12 months	Night sweats	1	2.0	0	0.0	0.2744
	Coughing	5	10.2	7	12.1	0.7607
	Fever	2	4.1	2	3.5	0.8634
	Nausea/Vomiting				N=57	
		2	4.1	2	3.5	0.8774
			N=50		N=54	
Post-delivery 15 months	Night sweats	1	2.0	0	0.0	0.2964
	Coughing	7	14.0	0	0.0	0.0044
	Fever	3	6.0	0	0.0	0.0678
	Nausea/Vomiting	0	0.0	1	1.9	0.3336
			N=42		N=49	
Post-delivery 18 months	Night sweats	1	2.4	0	0.0	0.2774
	Coughing	4	9.5	7	14.3	0.4873
	Fever	0	0.0	0	0.0	
	Nausea/Vomiting	0	0.0	0	0.0	

APPENDIX 18

Abnormalities on physical examination for all the mothers in Safety population who attended the visit

	Variable	Vitamin A N=58		Placebo N=55		P-value
		n	%	n	%	
Post-delivery 1 month	Anaemia /Jaundice	0	0.0	0	0.0	
	Lymphadenopathy	1	1.7	0	0.0	0.3280
	CVS	0	0.0	3	1.8	0.3674
	GIT	0	0.0	0	0.0	
	UG	N=57				
		1	1.8	0	0.0	0.0296
	CNS			N=54		
		0	0.0	1	1.9	0.3669
	ENT	0	0.0	2	3.6	0.2179
	Skin	0	0.0	1	1.8	0.3023
	Respiratory	0	0.0	0	0.0	
		N=66		N=74		
Post-delivery 3 months	Anaemia /Jaundice	0	0.0	0	0.0	
	Lymphadenopathy	0	0.0	1	1.4	0.3432
	CVS	0	0.0	0	0.0	
	GIT	0	0.0	0	0.0	
	UG	2	3.0	0	0.0	0.2059
	CNS	0	0.0	0	0.0	
	ENT	2	3.0	2	2.7	0.9075
	Skin	3	4.5	1	1.4	0.2575
	Respiratory	0	0.0	0	0.0	
		N=59		N=72		
Post-delivery 6 months	Anaemia/Jaundice	0	0.0	3	4.2	0.1127
	Lymphadenopathy	2	3.4	2	2.8	0.8395
	CVS	0	0.0	1	1.4	0.3635
	GIT			N=71		
		0	0.0	1	1.4	0.4300
	UG	0	0.0	0	0.0	
	CNS	0	0.0	1	1.4	0.3635
	ENT	1	1.7	1	1.4	0.8870
	Skin	0	0.0	3	4.2	0.1127
	Respiratory	0	0.0	1	1.4	0.3635
		N=57		N=62		
Post-delivery 9 months	Anaemia/Jaundice	N=56				
		0	0.0	1	1.6	0.3399
				N=63		
	Lymphadenopathy	1	1.8	0	0.0	0.2911
	CVS	0	0.0	0	0.0	
	GIT	0	0.0	1	1.6	0.3399
	UG	0	0.0	0	0.0	
	CNS	0	0.0	0	0.0	
				N=63		
	ENT	0	0.0	1	1.6	0.3395
	Skin	N=56		N=63		
		2	3.6	5	7.9	0.3124
				N=63		
	Respiratory	1	1.8	0	0.0	0.2911

			N=50		N=62	
Post-delivery 12 months	Anaemia/Jaundice				N=63	
		1	2.0	1	1.6	0.8687
	Lymphadenopathy	3	6.1	0	0.0	0.0506
	CVS	1	2.0	0	0.0	0.2633
	GIT	1	2.0	0	0.0	0.2633
	UG	0	0.0	0	0.0	
	CNS	0	0.0	1	1.6	0.3670
	ENT	0	0.0	0	0.0	
					N=63	
	Skin	4	8.0	0	0.0	0.0223
	Respiratory	1	2.0	0	0.0	0.2633
			N= 49		N=56	
Post-delivery 15 months	Anaemia/Jaundice	0	0.0	1	1.8	0.3473
	Lymphadenopathy	0	0.0	0	0.0	
					N=55	
	CVS	0	0.0	1	1.8	0.3429
			N=48			
	GIT	0	0.0	0	0.0	
	UG	0	0.0	0	0.0	
			N=48		N=55	
	CNS	0	0.0	0	0.0	
	ENT	0	0.0	1	1.8	0.3473
	Skin	2	4.1	3	5.4	0.7595
	Respiratory	0	0.0	1	1.8	0.3473
			N=42		N=48	
Post-delivery 18 months	Anaemia/Jaundice				N=49	
		0	0.0	3	6.1	0.1030
	Lymphadenopathy	1	2.4	0	0.0	0.2824
	CVS	0	0.0	1	2.1	0.3469
	GIT	0	0.0	0	0.0	
	UG	0	0.0	0	0.0	
	CNS		N=41			
		0	0.0	0	0.0	
	ENT	0	0.0	0.	0.0	
	Skin	0	0.0	4	8.2	0.0966
	Respiratory	0	0.0	0	0.0	

APPENDIX 19

Abnormalities on physical examination for all the infants in Safety population who attended the visit

	Variable	Vitamin A N=58 n	%	Placebo N=55 n	%	P-value
Post-delivery 1 month	General appearance		N=57			
		1	1.8	0	0.0	0.3238
	Skin	4	6.9	3	5.5	0.7506
	Eyes				N=54	
		0	0.0	0	0.0	
	Musculoskeletal				N=54	
		0	0.0	0	0.0	
	ENT		N=57		N=53	
		3	5.3	1	1.9	0.3445
Post-delivery 3 month			N=65		N=74	
	General appearance	5	7.7	5	6.8	0.8142
	Skin	5	7.7	7	9.5	0.7113
	Eyes	1	1.5	1	1.4	0.9264
	Musculoskeletal				N=73	
		0	0.0	0	0.0	
	ENT	4	6.2	6	8.1	0.5161
Post-delivery 6 month			N=59		N=69	
	General appearance	9	15.3	7	10.1	0.3836
	Skin	6	10.2	7	10.1	0.9963
	Eyes	1	1.7	0	0.0	0.2776
	Musculoskeletal	0	0.0	0	0.0	
	ENT	5	8.4	6	8.7	0.9645
Post-delivery 9 month			N=56		N=63	
	General appearance	5	9.1	5	7.9	0.8223
	Skin	6	10.7	6	9.5	0.8296
	Eyes	0	0.0	0	0.0	
	Musculoskeletal	0	0.0	0	0.0	
	ENT		N=55			
		2	3.6	5	7.9	0.3239
Post-delivery 12 month			N=49		N=59	
	General appearance		N=50			
		6	12.0	7	11.9	0.9826
	Skin				N=60	
		3	6.1	7	11.7	0.3195
	Eyes	2	4.1	0	0.0	0.1173
	Musculoskeletal	0	0.0	0	0.0	
	ENT	6	12.2	5	8.5	0.5190
Post-delivery 15 month			N=50		N=55	
	General appearance	5	10.0	3	5.5	0.3806
	Skin	8	16.0	0	0.0	0.0045
	Eyes		N=49			
		1	2.0	1	1.8	0.9342
	Musculoskeletal	1	2.0	0	0.0	0.2920
	ENT	2	4.0	2	3.6	0.9226
Post-delivery 18 month			N=42		N=49	
	General appearance	4	9.5	2	4.1	0.2930
	Skin	6	14.3	4	8.2	0.3519
	Eyes	0	0.0	1	2.0	0.3519
	Musculoskeletal	1	2.4	0	0.0	0.2774
	ENT	1	2.4	4	8.2	0.2275

APPENDIX 20

Vital signs for all the mothers in Safety population who attended the visit

Visit	Variable[unit]	Statistic	Vitamin A	Placebo	P-values
Post-delivery 1 month	Systolic blood pressure[mmHg]	N	58	57	
		Mean	120.9	122.6	0.4822
		SD	12.6	14.3	
		Min	90.0	100.0	
		Median	120.0	120.0	
		Max	160.0	190.0	
	Diastolic blood pressure[mmHg]	N	58	57	
		Mean	79.8	79.9	0.9652
		SD	9.7	11.0	
		Min	60.0	60.0	
		Median	80.0	80.0	
		Max	110.0	130.0	
	Heart rate[beats/min]	N	57	56	
		Mean	75.3	74.4	0.3818
		SD	6.4	4.6	
		Min	62.0	65.0	
		Median	76.0	75.0	
		Max	102.0	90.0	
Post-delivery 3 months	Systolic blood pressure[mmHg]	N	67	74	
		Mean	119.9	120.9	0.4997
		SD	6.6	9.3	
		Min	95.0	100.0	
		Median	120.0	120.0	
		Max	140.0	160.0	
	Diastolic blood pressure[mmHg]	N	67	74	
		Mean	79.2	79.5	0.7991
		SD	6.1	6.9	
		Min	60.0	60.0	
		Median	80.0	80.0	
		Max	95.0	100.0	
	Heart rate[beats/min]	N	67	74	
		Mean	75.2	74.9	0.7720
		SD	3.7	4.6	
		Min	66.0	60.0	
		Median	76.0	76.0	
		Max	84.0	84.0	
	Weight[kg]	N	56	63	
		Mean	62.6	59.7	0.1978
		SD	12.6	11.9	
		Min	41.5	41.0	
		Median	61.0	57.0	
		Max	98.5	94.5	
Post-delivery 6 month	Systolic blood pressure[mmHg]	N	58	70	
		Mean	120.5	119.8	0.6349
		SD	7.6	9.7	
		Min	110.0	100.0	
		Median	120.0	120.0	
		Max	155.0	160.0	
	Diastolic blood pressure[mmHg]	N	58	69	
		Mean	79.0	78.2	0.4371
		SD	5.5	6.1	
		Min	60.0	60.0	
		Median	80.0	80.0	
		Max	98.0	100.0	
	Heart rate[beats/min]	N	57	70	
		Mean	75.6	75.7	0.8887
		SD	3.5	4.8	
		Min	66.0	62.0	
		Median	76.0	76.0	
		Max	84.0	84.0	
	Weight[kg]	N	52	64	
		Mean	62.0	60.6	0.5785
		SD	12.9	13.8	
		Min	41.0	38.5	
		Median	60.0	56.3	
		Max	99.5	110.0	
		Mean	118.4	118.4	0.9691
		SD	5.8	7.7	

		Min	110.0	100.0	
		Median	120.0	120.0	
		Max	135.0	140.0	
	Diastolic blood pressure[mmHg]	N	57	61	
		Mean	78.2	77.5	0.4301
		SD	4.5	5.1	
		Min	70.0	60.0	
		Median	80.0	80.0	
		Max	90.0	90.0	
	Heart rate[beats/min]	N	56	61	
		Mean	76.1	77.2	0.3517
		SD	5.1	7.8	
		Min	65.0	60.0	
		Median	76.0	76.0	
		Max	88.0	120.0	
	Weight[kg]	N	54	60	
		Mean	62.5	60.9	0.5331
		SD	13.2	15.0	
		Min	42.5	40.0	
		Median	60.3	56.8	
		Max	100.0	111.5	
Post-delivery 12 months	Systolic blood pressure[mmHg]	N	51	63	
		Mean	115.4	117.0	0.4337
		SD	8.4	12.5	
		Min	100.0	100.0	
		Median	110.0	120.0	
		Max	150.0	200.0	
	Diastolic blood pressure[mmHg]	N	51	63	
		Mean	78.1	77.1	0.4057
		SD	4.7	7.6	
		Min	70.0	50.0	
		Median	80.0	80.0	
		Max	90.0	120.0	
	Heart rate[beats/min]	N	51	63	
		Mean	77.7	78.9	0.2878
		SD	7.1	5.3	
		Min	62.0	66.0	
		Median	76.0	76.0	
		Max	110.0	100.0	
	Weight [kg]	N	50	62	
		Mean	62.2	60.8	0.6045
		SD	13.5	14.5	
		Min	41.5	40.0	
		Median	59.5	55.8	
		Max	101.0	106.0	
Post-delivery 15 month	Systolic blood pressure[mmHg]	N	50	57	
		Mean	114.9	115.5	0.5824
		SD	6.2	5.1	
		Min	100.0	110.0	
		Median	110.0	120.0	
		Max	135.0	125.0	
	Diastolic blood pressure[mmHg]	N	50	57	
		Mean	77.2	77.8	0.4251
		SD	4.1	3.6	
		Min	70.0	70.0	
		Median	80.0	80.0	
		Max	85.0	85.0	
	Heart rate[beats/min]	N	50	57	
		Mean	78.8	80.2	0.3480
		SD	4.7	9.6	
		Min	70.0	62.0	
		Median	76.0	78.0	
		Max	86.0	140.0	
	Weight[kg]	N	50	58	
		Mean	60.7	61.7	0.7201
		SD	13.2	15.9	
		Min	40.0	40.0	
		Median	58.8	69.5	
		Max	102.0	106.0	
Post-delivery 18 months	Systolic blood pressure[mmHg]	N	42	49	

	Mean	113.3	114.4	0.4759
	SD	6.5	7.4	
	Min	100.0	100.0	
	Median	110.0	110.0	
	Max	140.0	140.0	
Diastolic blood pressure[mmHg]	N	42	49	
	Mean	76.7	75.9	0.5071
	SD	4.5	6.5	
	Min	60.0	60.0	
	Median	75.0	75.0	
	Max	88.0	95.0	
Heart rate[beats/min]	N	42	49	
	Mean	79.7	81.4	0.2388
	SD	6.7	7.0	
	Min	58.0	68.0	
	Median	84.0	84.0	
	Max	90.0	110.0	
Weight[kg]	N	42	48	
	Mean	62.7	61.0	0.5603
	SD	12.5	15.4	
	Min	44.0	40.5	
	Median	58.8	56.8	
	Max	98.6	106.0	

APPENDIX 21

Full blood and T-cell counts for all the mothers in Safety population who attended the visit

Visit	Variable[unit]	Statistic	Vitamin A	Placebo	P-value
Post-delivery 3 months	Haemoglobin[g/dl]	N	63	70	
		Mean	12.72	12.87	0.5592
		SD	1.53	1.26	
		Min	8.30	9.80	
		Median	12.90	12.80	
		Max	17.10	17.60	
	Haematocrit[l/l]	N	63	70	
		Mean	0.399	0.403	0.5271
		SD	0.041	0.037	
		Min	0.290	0.310	
		Median	0.400	0.400	
		Max	0.540	0.560	
	Red blood cells[10^9 cells/litre]	N	63	70	
		Mean	4.606	4.643	0.6478
		SD	0.482	0.441	
		Min	3.420	3.550	
		Median	4.580	4.650	
		Max	6.570	6.130	
	White blood cells[10^9 cells/litre]	N	63	70	
		Mean	5.67	5.48	0.5413
		SD	2.08	1.74	
		Min	2.50	2.40	
		Median	5.40	5.20	
		Max	14.30	12.10	
	Lymphocytes[10^9 cells/litre]	N	63	70	
		Mean	2.30	2.13	0.1977
		SD	0.80	0.76	
		Min	1.10	2.00	
		Median	2.10	2.00	
		Max	5.50	5.10	
	Neutrophils[10^9 cells/litre]	N	63	70	
		Mean	2.89	2.89	0.9764
		SD	1.60	1.35	
		Min	0.80	0.18	
		Median	2.60	2.60	
		Max	9.60	7.00	
	Monocytes[10^9 cells/litre]	N	63	70	
		Mean	0.335	0.275	0.0278
		SD	0.194	0.111	
		Min	0.110	0.050	
		Median	0.300	0.245	
		Max	1.260	0.750	
	Eosinophils[10^9 cells/litre]	N	63	70	
		Mean	0.203	0.111	0.0277
		SD	0.334	0.090	
		Min	0.000	0.010	
		Median	0.100	0.090	
		Max	2.130	0.410	
	Thrombocytes[10^9 cells/litre]	N	63	70	
		Mean	297.2	292.7	0.7065
		SD	76.1	63.8	
		Min	141.0	182.0	
		Median	281.0	294.5	
		Max	513.0	443.0	
Post-delivery 6 months	Haemoglobin[g/dl]	N	58	65	
		Mean	13.01	12.76	0.2551
		SD	1.21	1.27	
		Min	9.90	9.20	
		Median	13.15	12.70	
		Max	15.90	15.10	
	Haematocrit[l/l]	N	58	65	
		Mean	0.406	0.396	0.1151
		SD	0.039	0.036	
		Min	0.300	0.290	
		Median	0.410	0.400	

		Max	0.490	0.470	
	Red blood cells[10^9 cells/litre]	N	58	65	
		Mean	4.624	4.521	0.1776
		SD	0.415	0.422	
		Min	3.770	3.050	
		Median	4.655	4.470	
		Max	5.560	5.470	
	White blood cells[10^9 cells/litre]	N	58	65	
		Mean	5.55	5.47	0.7979
		SD	1.62	1.75	
		Min	3.00	0.18	
		Median	5.30	5.40	
		Max	10.90	10.20	
	Lymphocytes[10^9 cells/litre]	N	58	65	
		Mean	2.15	2.02	0.3500
		SD	0.65	0.83	
		Min	0.70	0.70	
		Median	2.10	1.90	
		Max	3.60	5.30	
	Neutrophils[10^9 cells/litre]	N	58	65	
		Mean	2.94	3.02	0.7019
		SD	1.22	1.04	
		Min	1.20	1.30	
		Median	2.75	3.10	
		Max	6.40	6.20	
	Monocytes[10^9 cells/litre]	N	58	65	
		Mean	0.292	0.288	0.8107
		SD	0.090	0.123	
		Min	0.110	0.130	
		Median	0.280	0.250	
		Max	0.560	0.870	
	Eosinophils[10^9 cells/litre]	N	58	65	
		Mean	0.132	0.157	0.6269
		SD	0.186	0.340	
		Min	0.000	0.000	
		Median	0.060	0.060	
		Max	1.160	2.560	
	Thrombocytes[10^9 cells/litre]	N	58	65	
		Mean	291.9	285.9	0.6157
		SD	70.1	60.5	
		Min	134.0	177.0	
		Median	287.5	282.0	
		Max	485.0	474.0	
Post-delivery 12 months	Haemoglobin[g/dl]	N	50	63	
		Mean	12.92	13.04	0.7192
		SD	1.64	1.65	
		Min	7.70	9.90	
		Median	13.00	13.10	
		Max	18.06	20.00	
	Haematocrit[l/l]	N	50	63	
		Mean	0.401	0.404	0.8005
		SD	0.046	0.047	
		Min	0.250	0.320	.
		Median	0.400	0.400	
		Max	0.550	0.580	
	Red blood cells[10^9 cells/litre]	N	50	63	
		Mean	4.530	4.575	0.6456
		SD	0.532	0.518	
		Min	2.830	3.450	
		Median	4.560	4.510	
		Max	6.220	6.260	
	White blood cells[10^9 cells/litre]	N	50	63	
		Mean	5.34	5.27	0.7682
		SD	1.82	1.41	
		Min	2.10	2.50	
		Median	4.85	5.10	
		Max	10.60	9.20	
	Lymphocytes[10^9 cells/litre]	N	50	63	
		Mean	1.89	2.02	0.3407
		SD	0.58	0.75	

		Min	1.00	0.80	
		Median	1.80	1.90	
		Max	3.70	4.40	
	Neutrophils[10^9 cells/litre]	N	50	63	
		Mean	3.01	2.82	0.4211
		SD	1.43	1.09	
		Min	0.80	1.00	
		Median	2.60	2.70	
		Max	6.30	6.40	
	Monocytes[10^9 cells/litre]	N	50	63	
		Mean	0.315	0.287	0.1999
		SD	0.132	0.101	
		Min	0.140	0.130	
		Median	0.280	0.270	
		Max	0.830	0.600	
	Eosinophils[10^9 cells/litre]	N	50	63	
		Mean	0.089	0.106	0.3207
		SD	0.081	0.100	
		Min	0.002	0.000	
		Median	0.060	0.070	
		Max	0.310	0.430	
	Thrombocytes[10^9 cells/litre]	N	50	63	
		Mean	279.8	284.9	0.7167
		SD	80.1	68.3	
		Min	79.0	114.0	
		Median	282.0	278.0	
		Max	464.0	502.0	
Post-delivery 18 months	Haemoglobin[g/dl]	N	42	47	
		Mean	12.70	12.45	0.4234
		SD	1.35	1.57	
		Min	9.10	8.30	
		Median	12.95	12.60	
		Max	15.70	15.50	
	Haematocrit[l/l]	N	42	47	
		Mean	0.385	0.379	0.4661
		SD	0.041	0.042	
		Min	0.280	0.280	
		Median	0.395	0.390	
		Max	0.490	0.450	
	Red blood cells[10^9 cells/litre]	N	42	47	
		Mean	4.390	4.319	0.4968
		SD	0.476	0.497	
		Min	3.140	3.090	
		Median	4.445	4.330	
		Max	5.280	5.440	
	White blood cells[10^9 cells/litre]	N	42	47	
		Mean	5.59	5.19	0.2471
		SD	1.78	1.51	
		Min	3.10	3.00	
		Median	5.10	4.90	
		Max	10.20	9.80	
	Lymphocytes[10^9 cells/litre]	N	42	47	
		Mean	2.00	1.82	0.1917
		SD	0.63	0.65	
		Min	1.00	0.40	
		Median	1.95	1.70	
		Max	3.60	3.50	
	Neutrophils[10^9 cells/litre]	N	42	47	
		Mean	3.12	2.91	0.4595
		SD	1.44	1.21	
		Min	1.30	1.10	
		Median	2.60	2.60	
		Max	6.80	6.30	
	Monocytes[10^9 cells/litre]	N	41	47	
		Mean	0.321	0.278	0.0525
		SD	0.107	0.101	
		Min	0.140	0.160	
		Median	0.310	0.240	
		Max	0.620	0.700	
	Eosinophils[10^9 cells/litre]	N	41	47	

		Mean	0.117	0.131	0.6047
		SD	0.114	0.139	
		Min	0.010	0.000	
		Median	0.080	0.070	
		Max	0.500	0.560	
	Thrombocytes[10^9 cells/litre]	N	42	47	
		Mean	303.2	308.5	0.7253
		SD	71.3	70.8	
		Min	188.0	172.0	
		Median	304.5	300.0	
		Max	507.0	550.0	
Post-delivery 3 months	CD4 counts[10^9 cells/litre]	N	65	72	
		Mean	0.538	0.518	0.7051
		SD	0.328	0.278	
		Min	0.100	0.080	
		Median	0.490	0.465	
		Max	2.260	1.660	
	CD8 counts [10^9 cells/litre]	N	65	72	
		Mean	1.13	1.08	0.5606
		SD	0.48	0.52	
		Min	0.39	0.45	
		Median	1.05	0.96	
		Max	2.77	3.03	
	CD4/CD8 ratio	N	65	72	
		Mean	0.491	0.554	0.2368
		SD	0.268	0.341	
		Min	0.110	0.050	
		Median	0.460	0.470	
		Max	1.33	1.820	
Post-delivery 6 months	CD4 counts[10^9 cells/litre]	N	56	64	
		Mean	0.479	0.516	0.4945
		SD	0.257	0.332	
		Min	0.040	0.070	
		Median	0.455	0.430	
		Max	1.260	2.040	
	CD8 counts[10^9 cells/litre]	N	56	64	
		Mean	1.10	0.98	0.1683
		SD	0.42	0.50	
		Min	0.31	0.32	
		Median	1.06	0.91	
		Max	2.24	2.94	
	CD4/CD8 ratio	N	56	64	
		Mean	0.478	0.598	0.0587
		SD	0.275	0.395	
		Min	0.070	0.050	
		Median	0.396	0.480	
		Max	1.060	2.110	
Post-delivery 12 months	CD4 counts[10^9 cells/litre]	N	50	62	
		Mean	0.427	0.454	0.5068
		SD	0.202	0.227	
		Min	0.130	0.050	
		Median	0.405	0.440	
		Max	0.820	1.060	
	CD8 counts[10^9 cells/litre]	N	50	62	
		Mean	0.93	1.00	0.3778
		SD	0.32	0.52	
		Min	0.45	0.39	
		Median	0.88	0.85	
		Max	1.90	3.06	
	CD4/CD8 ratio	N	50	62	
		Mean	0.497	0.543	0.4506
		SD	0.273	0.349	
		Min	0.120	0.020	
		Median	0.430	0.445	
		Max	1.180	1.780	
Post-delivery 18 months	CD4 counts[10^9 cells/litre]	N	42	46	
		Mean	0.406	0.414	0.8717
		SD	0.239	0.209	
		Min	0.030	0.060	
		Median	0.365	0.405	

		Mean	0.117	0.131	0.6047
		SD	0.114	0.139	
		Min	0.010	0.000	
		Median	0.080	0.070	
		Max	0.500	0.560	
	Thrombocytes[10^9 cells/litre]	N	42	47	
		Mean	303.2	308.5	0.7253
		SD	71.3	70.8	
		Min	188.0	172.0	
		Median	304.5	300.0	
		Max	507.0	550.0	
Post-delivery 3 months	CD4 counts[10^9 cells/litre]	N	65	72	
		Mean	0.538	0.518	0.7051
		SD	0.328	0.278	
		Min	0.100	0.080	
		Median	0.490	0.465	
		Max	2.260	1.660	
	CD8 counts [10^9 cells/litre]	N	65	72	
		Mean	1.13	1.08	0.5606
		SD	0.48	0.52	
		Min	0.39	0.45	
		Median	1.05	0.96	
		Max	2.77	3.03	
	CD4/CD8 ratio	N	65	72	
		Mean	0.491	0.554	0.2368
		SD	0.268	0.341	
		Min	0.110	0.050	
		Median	0.460	0.470	
		Max	1.33	1.820	
Post-delivery 6 months	CD4 counts[10^9 cells/litre]	N	56	64	
		Mean	0.479	0.516	0.4945
		SD	0.257	0.332	
		Min	0.040	0.070	
		Median	0.455	0.430	
		Max	1.260	2.040	
	CD8 counts[10^9 cells/litre]	N	56	64	
		Mean	1.10	0.98	0.1683
		SD	0.42	0.50	
		Min	0.31	0.32	
		Median	1.06	0.91	
		Max	2.24	2.94	
	CD4/CD8 ratio	N	56	64	
		Mean	0.478	0.598	0.0587
		SD	0.275	0.395	
		Min	0.070	0.050	
		Median	0.396	0.480	
		Max	1.060	2.110	
Post-delivery 12 months	CD4 counts[10^9 cells/litre]	N	50	62	
		Mean	0.427	0.454	0.5068
		SD	0.202	0.227	
		Min	0.130	0.050	
		Median	0.405	0.440	
		Max	0.820	1.060	
	CD8 counts[10^9 cells/litre]	N	50	62	
		Mean	0.93	1.00	0.3778
		SD	0.32	0.52	
		Min	0.45	0.39	
		Median	0.88	0.85	
		Max	1.90	3.06	
	CD4/CD8 ratio	N	50	62	
		Mean	0.497	0.543	0.4506
		SD	0.273	0.349	
		Min	0.120	0.020	
		Median	0.430	0.445	
		Max	1.180	1.780	
Post-delivery 18 months	CD4 counts[10^9 cells/litre]	N	42	46	
		Mean	0.406	0.414	0.8717
		SD	0.239	0.209	
		Min	0.030	0.060	
		Median	0.365	0.405	

	Max	0.990	1.000	
CD8 counts[10^9 cells/litre]	N	42	46	
	Mean	1.05	0.96	0.3472
	SD	0.43	0.46	
	Min	0.54	0.19	
	Median	0.94	0.80	
	Max	2.74	2.11	
CD4/CD8 ratio	N	42	46	
	Mean	0.428	0.483	0.3572
	SD	0.284	0.266	
	Min	0.030	0.050	
	Median	0.345	0.430	
	Max	1.300	1.480	

APPENDIX 22

Full blood and T-cell counts for all the infants in Safety population who attended the visit

Visit	Variable[unit]	Statistic	Vitamin A	Placebo	P-value
Post-delivery 3 months	Haemoglobin[g/dl]	N	59	63	
		Mean	10.20	10.12	0.6413
		SD	0.91	1.00	
		Min	7.60	7.20	
		Median	10.30	10.20	
		Max	13.70	12.10	
	Haematocrit[l/l]	N	59	63	
		Mean	0.310	0.402	0.3508
		SD	0.029	0.758	
		Min	0.250	0.230	
		Median	0.310	0.310	
		Max	0.430	6.320	
	Red blood cells[10^9 cells/litre]	N	59	63	
		Mean	3.865	3.832	0.6735
		SD	0.385	0.463	
		Min	3.120	2.890	
		Median	3.860	3.820	
		Max	4.900	5.280	
	White blood cells[10^9 cells/litre]	N	59	63	
		Mean	11.24	10.26	0.1814
		SD	4.55	3.42	
		Min	5.60	4.00	
		Median	10.60	10.10	
		Max	32.60	19.60	
	Lymphocytes[10^9 cells/litre]	N	59	63	
		Mean	6.91	6.33	0.2118
		SD	2.75	2.33	
		Min	1.80	0.10	
		Median	6.50	6.20	
		Max	18.70	11.40	
	Neutrophils[10^9 cells/litre]	N	59	63	
		Mean	2.87	2.62	0.3669
		SD	1.65	1.45	
		Min	0.60	0.60	
		Median	2.50	2.10	
		Max	8.70	8.00	
	Monocytes[10^9 cells/litre]	N	59	63	
		Mean	0.896	0.772	0.1464
		SD	0.552	0.366	
		Min	0.350	0.210	
		Median	0.780	0.660	
		Max	3.880	2.230	
	Eosinophils[10^9 cells/litre]	N	59	63	
		Mean	0.419	0.305	0.0570
		SD	0.400	0.242	
		Min	0.010	0.000	
		Median	0.270	0.210	
		Max	1.940	1.220	
	Thrombocytes[10^9 cells/litre]	N	59	63	
		Mean	399.7	380.3	0.4354
		SD	140.9	134.0	
		Min	29.0	54.0	
		Median	417.0	401.0	
		Max	841.0	617.0	
Post-delivery 6 months	Haemoglobin[g/dl]	N	59	61	
		Mean	10.57	10.66	0.6397
		SD	0.86	1.16	
		Min	8.10	7.30	
		Median	10.50	10.60	
		Max	12.20	13.20	
	Haematocrit[l/l]	N	59	61	
		Mean	0.322	0.322	0.9321
		SD	0.0260	0.030	
		Min	0.260	0.240	
		Median	0.320	0.320	

		Max	0.380	0.400	
	Red blood cells[10^9 cells/litre]	N	59	61	
		Mean	4.341	4.332	0.9024
		SD	0.393	0.412	
		Min	3.510	3.350	
		Median	4.310	4.590	
		Max	5.260	5.360	
	White blood cells[10^9 cells/litre]	N	59	61	
		Mean	10.87	10.16	0.2311
		SD	3.26	3.18	
		Min	5.00	4.00	
		Median	10.80	9.80	
		Max	22.50	22.30	
	Lymphocytes[10^9 cells/litre]	N	59	61	
		Mean	6.72	6.27	0.2925
		SD	2.31	2.36	
		Min	2.50	0.80	
		Median	6.20	6.10	
		Max	12.00	13.70	
	Neutrophils[10^9 cells/litre]	N	59	61	
		Mean	2.880	2.81	0.7850
		SD	1.423	1.31	
		Min	1.000	0.20	
		Median	2.500	2.50	
		Max	9.100	7.00	
	Monocytes[10^9 cells/litre]	N	59	61	
		Mean	0.846	0.721	0.0870
		SD	0.430	0.365	
		Min	0.250	0.200	
		Median	0.710	0.660	
		Max	2.220	2.040	
	Eosinophils[10^9 cells/litre]	N	59	61	
		Mean	0.309	2.811	0.6911
		SD	3.295	1.315	
		Min	0.030	0.200	
		Median	0.200	2.500	
		Max	1.660	7.000	
	Thrombocytes[10^9 cells/litre]	N	59	61	
		Mean	394.3	372.8	0.4015
		SD	142.3	137.9	
		Min	85.0	63.0	
		Median	380.0	368.0	
		Max	754.0	735.0	
Post-delivery 12 months	Haemoglobin[g/dl]	N	51	63	
		Mean	10.85	10.99	0.4526
		SD	1.09	0.91	
		Min	7.46	8.60	
		Median	11.00	11.00	
		Max	12.80	12.90	
	Haematocrit[l/l]	N	51	63	
		Mean	0.335	0.335	0.9842
		SD	0.028	0.028	
		Min	0.260	0.280	
		Median	0.340	0.330	
		Max	0.400	0.400	
	Red blood cells[10^9 cells/litre]	N	51	63	
		Mean	4.518	4.532	0.8388
		SD	0.371	0.364	
		Min	3.760	3.700	
		Median	4.530	4.540	
		Max	5.310	5.230	
	White blood cells[10^9 cells/litre]	N	51	63	
		Mean	11.00	10.14	0.2016
		SD	4.11	3.05	
		Min	5.10	4.90	
		Median	9.50	9.70	
		Max	23.20	22.10	
	Lymphocytes[10^9 cells/litre]	N	51	63	
		Mean	6.16	6.05	0.7960
		SD	2.18	2.45	

		Min	2.50	1.90	
		Median	6.00	5.80	
		Max	13.50	15.00	
	Neutrophils[10^9 cells/litre]	N	51	63	
		Mean	3.39	3.08	0.3558
		SD	2.15	1.40	
		Min	0.80	0.80	
		Median	2.80	3.00	
		Max	10.80	9.50	
	Monocytes[10^9 cells/litre]	N	51	63	
		Mean	1.066	0.658	0.0620
		SD	1.697	0.251	
		Min	0.290	0.320	
		Median	0.680	0.610	
		Max	1.240	1.550	
	Eosinophils[10^9 cells/litre]	N	51	63	
		Mean	0.247	0.244	0.9546
		SD	0.237	0.273	
		Min	0.000	0.020	
		Median	0.200	0.170	
		Max	1.170	1.520	
	Thrombocytes[10^9 cells/litre]	N	51	63	
		Mean	384.1	394.9	0.6673
		SD	138.4	126.8	
		Min	55.0	64.0	
		Median	384.0	389.0	
		Max	704.0	756.0	
Post-delivery 18 months	Haemoglobin[g/dl]	N	41	48	
		Mean	10.73	10.91	0.4052
		SD	0.98	1.00	
		Min	8.50	8.30	
		Median	11.00	10.95	
		Max	12.20	13.10	
	Haematocrit[l/l]	N	41	48	
		Mean	0.327	0.331	0.4983
		SD	0.023	0.028	
		Min	0.270	0.270	
		Median	0.330	0.330	
		Max	0.370	0.380	
	Red blood cells[10^9 cells/litre]	N	41	48	
		Mean	4.411	4.533	0.1342
		SD	0.362	0.392	
		Min	3.730	3.610	
		Median	4.450	4.525	
		Max	5.080	5.370	
	White blood cells[10^9 cells/litre]	N	41	48	
		Mean	9.78	9.97	0.7716
		SD	2.80	3.29	
		Min	4.30	5.10	
		Median	9.20	9.50	
		Max	15.10	23.30	
	Lymphocytes[10^9 cells/litre]	N	41	48	
		Mean	5.45	5.73	0.5197
		SD	1.99	2.05	
		Min	0.60	2.20	
		Median	5.30	5.20	
		Max	9.50	11.60	
	Neutrophils[10^9 cells/litre]	N	41	48	
		Mean	2.95	3.27	0.2796
		SD	1.43	1.37	
		Min	0.40	1.10	
		Median	2.50	3.20	
		Max	6.90	8.30	
	Monocytes[10^9 cells/litre]	N	41	48	
		Mean	0.662	0.630	0.6755
		SD	0.379	0.354	
		Min	0.220	0.230	
		Median	0.570	0.545	
		Max	2.530	2.610	
	Eosinophils[10^9 cells/litre]	N	41	48	

		Mean	0.325	0.295	0.6448
		SD	0.340	0.279	
		Min	0.020	0.200	
		Median	0.190	0.220	
		Max	1.710	1.490	
	Thrombocytes[10^9 cells/litre]	N	41	48	
		Mean	425.2	436.0	0.7175
		SD	157.1	123.6	
		Min	179.0	211.0	
		Median	400.0	421.0	
		Max	904.0	879.0	
Post-delivery 3 months	CD4 counts[10^9 cells/litre]	N	54	57	
		Mean	2.419	2.267	0.4383
		SD	1.070	0.989	
		Min	0.720	0.300	
		Median	2.270	2.080	
		Max	6.530	4.770	
	CD8 counts[10^9 cells/litre]	N	54	57	
		Mean	1.67	1.44	0.2770
		SD	1.19	1.01	
		Min	0.36	0.26	
		Median	1.48	1.12	
		Max	6.62	5.43	
	CD4/CD8 ratio	N	54	57	
		Mean	2.480	2.049	0.9974
		SD	1.257	1.373	
		Min	0.210	0.340	
		Median	2.030	1.830	
		Max	5.240	7.890	
Post-delivery 6 months	CD4 counts[10^9 cells/litre]	N	56	56	
		Mean	2.426	2.224	0.2568
		SD	0.951	0.928	
		Min	0.190	0.290	
		Median	2.510	2.105	
		Max	4.380	5.600	
	CD8 counts [10^9 cells/litre]	N	56	56	
		Mean	1.50	1.49	0.9477
		SD	1.04	1.09	
		Min	0.46	0.20	
		Median	1.29	1.09	
		Max	6.55	5.27	
	CD4/CD8 ratio	N	55	55	
		Mean	2.039	2.051	0.9573
		SD	1.035	1.300	
		Min	0.140	0.270	
		Median	2.040	1.820	
		Max	5.160	6.870	
Post-delivery 12 months	CD4 counts[10^9 cells/litre]	N	50	62	
		Mean	2.146	2.121	0.9032
		SD	0.997	1.122	
		Min	0.350	0.640	
		Median	2.070	1.950	
		Max	4.700	6.850	
	CD8 counts[10^9 cells/litre]	N	50	62	
		Mean	1.68	1.47	0.2851
		SD	1.13	0.95	
		Min	0.48	0.40	
		Median	1.44	1.14	
		Max	7.03	5.20	
	CD4/CD8 ratio	N	50	62	
		Mean	1.651	1.742	0.5968
		SD	0.931	0.862	
		Min	0.240	0.270	
		Median	1.540	1.700	
		Max	3.920	4.260	
Post-delivery 18 months	CD4 counts[10^9 cells/litre]	N	40	48	
		Mean	1.778	1.954	0.2992
		SD	0.821	0.756	
		Min	0.290	0.630	
		Median	1.880	1.895	

	Max	3.680	3.930	
CD8 counts[10^9 cells/litre]	N	40	48	
	Mean	1.59	1.18	0.5764
	SD	0.79	0.98	
	Min	0.39	0.35	
	Median	1.49	1.26	
	Max	4.03	6.16	
CD4/CD8 ratio	N	40	48	
	Mean	1.332	1.633	0.0571
	SD	0.671	0.774	
	Min	0.190	0.200	
	Median	1.420	1.520	
	Max	2.760	3.930	

APPENDIX 23

Infants' developmental characteristics for all the infants in Safety population who attended the visit

Visit	Variable[unit]	Statistic	Vitamin A	Placebo	P-value
Post-delivery 1 month	Length [cm]	N	58	54	
		Mean	53.5	54.6	0.2194
		SD	4.4	4.7	
		Min	42.0	43.0	
		Median	53.0	55.0	
		Max	64.0	69.5	
	Head circumference[cm]	N	58	53	
		Mean	37.7	37.5	0.6123
		SD	2.1	2.7	
		Min	32.0	32.0	
		Median	38.0	38.0	
		Max	43.0	45.0	
	Heart rate[beats/min]	N	55	55	
		Mean	140.3	141.1	0.7134
		SD	11.0	11.3	
		Min	102.0	105.0	
		Median	146.0	146.0	
		Max	156.0	180.0	
	Weight[kg]	N	58	54	
		Mean	4.0	4.2	0.5252
		SD	0.9	1.1	
		Min	2.1	2.0	
		Median	4.0	4.1	
		Max	6.8	6.3	
Post-delivery 3 month	Length [cm]	N	63	73	
		Mean	60.2	60.4	0.7835
		SD	4.3	4.8	
		Min	50.0	45.0	
		Median	60.0	61.0	
		Max	70.0	71.0	
	Head circumference[cm]	N	62	71	
		Mean	40.7	40.3	0.2524
		SD	2.0	2.1	
		Min	36.5	34.0	
		Median	41.0	40.0	
		Max	47.0	44.0	
	Heart rate[beats/min]	N	63	73	
		Mean	138.6	139.0	0.8295
		SD	10.3	10.5	
		Min	110.0	110.0	
		Median	146.0	146.0	
		Max	148.0	168.0	
	Weight[kg]	N	65	73	
		Mean	5.8	5.7	0.5518
		SD	1.1	1.3	
		Min	3.7	2.8	
		Median	5.9	5.7	
		Max	9.5	10.1	
Post-delivery 6 month	Length [cm]	N	57	67	
		Mean	66.7	67.1	0.6146
		SD	4.4	4.5	
		Min	57.0	56.0	
		Median	67.0	67.5	
		Max	79.0	77.0	
	Head circumference[cm]	N	57	66	
		Mean	43.3	43.3	0.8847
		SD	1.8	1.9	
		Min	39.0	38.5	
		Median	43.5	43.0	
		Max	48.0	47.0	
	Heart rate[beats/min]	N	57	68	
		Mean	134.8	133.2	0.4955
		SD	12.6	14.0	
		Min	104.0	100.0	
		Median	140.0	138.0	
		Max	156.0	146.0	
	Weight[kg]	N	58	68	
		Mean	7.2	7.3	0.8431

		SD	1.2	1.4	
		Min	4.7	3.4	
		Median	7.1	7.3	
		Max	10.8	10.7	
Post-delivery 9 month	Length [cm]	N	56	64	
		Mean	71.5	72.3	0.3093
		SD	4.7	4.0	
		Min	58.0	63.0	
		Median	71.5	72.0	
		Max	80.5	81.0	
	Head circumference[cm]	N	56	63	
		Mean	45.5	45.3	0.5612
		SD	2.0	1.8	
		Min	41.0	42.0	
		Median	46.0	45.0	
		Max	49.1	49.0	
	Heart rate[beats/min]	N	53	64	
		Mean	129.2	129.8	0.8393
		SD	16.2	16.4	
		Min	94.0	100.0	
		Median	132.0	130.0	
		Max	146.0	148.0	
	Weight[kg]	N	55	64	
		Mean	8.1	8.4	0.2542
		SD	1.3	1.4	
		Min	4.8	5.5	
		Median	7.9	8.5	
		Max	11.2	11.8	
Post-delivery 12 month	Length [cm]	N	50	61	
		Mean	75.7	76.4	0.3914
		SD	4.0	4.4	
		Min	68.0	66.0	
		Median	75.0	77.5	
		Max	87.0	89.0	
	Head circumference[cm]	N	50	61	
		Mean	46.8	46.9	0.8289
		SD	1.9	1.7	
		Min	42.0	44.0	
		Median	47.0	47.0	
		Max	50.7	51.0	
	Heart rate[beats/min]	N	47	61	
		Mean	120.8	122.4	0.6647
		SD	17.1	20.0	
		Min	100.0	92.0	
		Median	110.0	118.0	
		Max	146.0	196.0	
	Weight[kg]	N	50	61	
		Mean	8.9	9.3	0.1223
		SD	1.4	1.5	
		Min	5.2	6.2	
		Median	8.6	9.3	
		Max	11.7	13.1	
Post-delivery 15 month	Length [cm]	N	49	56	
		Mean	79.7	79.8	0.9180
		SD	4.8	3.9	
		Min	70.9	71.0	
		Median	80.5	80.0	
		Max	89.0	89.0	
	Head circumference[cm]	N	49	56	
		Mean	47.9	47.7	0.4730
		SD	1.5	2.1	
		Min	44.0	40.5	
		Median	48.0	48.0	
		Max	51.0	52.5	
	Heart rate[beats/min]	N	49	56	
		Mean	118.4	118.1	0.9116
		SD	18.1	16.7	
		Min	86.0	96.0	
		Median	110.0	110.0	
		Max	152.0	146.0	

	Weight[kg]	N	49	56	
		Mean	9.7	10.1	0.1788
		SD	1.4	1.5	
		Min	6.7	6.4	
		Median	9.4	10.3	
		Max	12.5	13.1	
Post-delivery 18 month	Length [cm]	N	42	48	
		Mean	82.7	82.9	0.7983
		SD	1.3	3.8	
		Min	74.5	75.8	
		Median	83.0	82.5	
		Max	89.5	91.0	
	Head circumference[cm]	N	42	48	
		Mean	49.3	49.1	0.6287
		SD	1.8	2.2	
		Min	44.5	40.0	
		Median	49.5	49.5	
		Max	52.5	53.0	
	Heart rate[beats/min]	N	40	48	
		Mean	108.8	107.2	0.4912
		SD	8.1	13.0	
		Min	92.0	86.0	
		Median	110.0	110.0	
		Max	126.0	146.0	
	Weight[kg]	N	42	48	
		Mean	10.2	10.5	0.3808
		SD	1.3	1.4	
		Min	7.5	7.6	
		Median	10.0	10.6	
		Max	13.5	13.5	

APPENDIX 24

HIV symptoms on medical history for all the mothers in ITT population who attended the visit

Visit	Variable	Vitamin A N=56		Placebo N=56		P-value
		n	%	n	%	
Post-natal 1 months	Night sweats	0	0.0	0	0.0	
	Coughing	1	1.8	0	0.0	0.3151
	Fever	1	1.8	0	0.0	0.3151
	Nausea/Vomiting	0	0.0	0	0.0	
	Headache	5	8.9	3	5.4	0.4631
	Confusion	1	1.8	0	0.0	0.3151
			N=63		N=74	
Post-natal 3 months	Night sweats	2	3.2	1	1.4	0.4674
	Coughing	1	1.6	3	4.1	0.3927
	Fever	2	3.2	0	0.0	0.1226
	Nausea/Vomiting	0	0.0	0	0.0	
	Headache	2	3.2	4	5.4	0.5248
	Confusion	0	0.0	0	0.0	
			N=55		N=70	
Post-natal 6 months	Night sweats	2	3.6	0	0.0	0.1078
	Coughing	2	3.6	2	2.9	0.8057
	Fever	0	0.0	1	1.4	0.3735
	Nausea/Vomiting	0	0.0	0	0.0	
	Headache	0	0.0	3	4.3	0.1202
	Confusion	0	0.0	0	0.0	
			N=54		N=62	
Post-natal 9 months	Night sweats		N=53			
		1	1.9	0	0.0	0.2819
	Coughing	3	5.6	1	1.6	0.2457
	Fever	2	3.7	2	3.2	0.8881
	Nausea/Vomiting	0	0.0	0	0.0	
	Headache	4	7.4	4	6.5	0.8394
	Confusion	0	0.0	2	3.2	0.1871
			N= 50		N=60	
Post-natal 12 months	Night sweats	0	0.0	0	0.0	
	Coughing	2	4.0	0	0.0	0.1179
	Fever	1	2.0	0	0.0	0.2711
	Nausea/Vomiting	0	0.0	0	0.0	
	Headache	4	8.0	2	3.3	0.2832
	Confusion	0	0.0	1	1.7	0.3639
			N=47		N=54	
Post-natal 15 months	Night sweats	0	0.0	0	0.0	
	Coughing	0	0.0	1	1.9	0.3485
	Fever	0	0.0	1	1.9	0.3485
	Nausea/Vomiting	0	0.0	0	0.0	
	Headache	0	0.0	2	3.7	0.1827
	Confusion	0	0.0	0	0.0	
			N=41		N=49	
Post-natal 18 months	Night sweats	0	0.0	0	0.0	
	Coughing	1	2.4	5	10.2	0.1414
	Fever	0	0.0	0	0.0	
	Nausea/Vomiting	0	0.0	0	0.0	
	Headache	3	7.3	3	6.1	0.8210
	Confusion	0	0.0	0	0.0	

APPENDIX 25

HIV symptoms on medical history for all the infants in ITT population who attended the visit

Visit	Variable	Vitamin A n=50		Placebo n=51		P-value
		n	%	N	%	
Post-natal 1 months	Night sweats	0	0.0	0	0.0	
	Coughing	1	2.0	3	5.9	0.3172
	Fever	1	2.0	2	3.9	0.5695
	Nausea/Vomiting	1	2.0	1	2.0	0.9887
			N=64		N=74	
Post-natal 3 months	Night sweats	3	4.4	0	0.0	0.0597
	Coughing	7	10.9	6	8.1	0.5704
	Fever	3	4.4	2	2.7	0.5338
	Nausea/Vomiting	2	3.1	1	1.4	0.4837
			N=56		N=69	
Post-natal 6 months	Night sweats	1	1.8	0	0.0	0.2651
	Coughing	9	16.1	9	13.0	0.6316
	Fever	3	5.4	6	8.7	0.4727
	Nausea/Vomiting	2	3.6	2	2.9	0.8317
			N=54		N=63	
Post-natal 9 months	Night sweats	1	1.9	2	3.2	0.6518
	Coughing	11	20.4	9	14.3	0.3835
	Fever	4	7.4	3	4.8	0.5475
	Nausea/Vomiting	2	3.9	2	3.2	0.8294
			N=49		N=58	
Post-natal 12 months	Night sweats	1	2.0	0	0.0	0.2744
	Coughing	5	10.2	7	12.1	0.7607
	Fever	2	4.1	2	3.5	0.8634
	Nausea/Vomiting	2	4.1	2	N=57 3.5	0.8774
			N=48		N=54	
Post-natal 15 months	Night sweats	1	2.1	0	0.0	0.2865
	Coughing	7	14.6	0	0.0	0.0036
	Fever	3	6.3	0	0.0	0.0622
	Nausea/Vomiting	0	0.0	1	1.9	0.3434
			N = 41		N=49	
Post-natal 18 months	Night sweats	1	2.4	0	0.0	0.2716
	Coughing	4	9.8	7	14.3	0.5234
	Fever	0	0.0	0	0.0	
	Nausea/Vomiting	0	0.0	0	0.0	

APPENDIX 26

Abnormalities on physical examinations for all the mothers in ITT population who attended the visit

Visit	Variable	Vitamin A N=50		Placebo N=50		P-value
		n	%	n	%	
Post-natal 1 month	Anaemia /Jaundice	0	0.0	0	0.0	
	Lymphadenopathy	0	0.0	0	0.0	
	CVS	0	0.0	1	2.0	0.3679
	GIT	0	0.0	0	0.0	
	UG		N=49			
		1	2.0	0	0.0	0.0973
	CNS				N=49	
		0	0.0	1	2.0	0.3678
	ENT		N=49			
		0	0.0	2	4.0	0.2242
	Skin	0	0.0	1	2.0	0.3149
	Respiratory	0	0.0	0	0.0	
			N=64		N=74	
Post-natal 3 months	Anaemia/Jaundice	0	0.0	0	0.0	
	Lymphadenopathy	0	0.0	1	1.4	0.3506
	CVS	0	0.0	0	0.0	
	GIT	0	0.0	0	0.0	
	UG	2	3.1	0	0.0	0.1888
	CNS	0	0.0	0	0.0	
	ENT	2	3.1	2	2.7	0.8828
	Skin	3	4.7	1	1.4	0.2440
	Respiratory	0	0.0	0	0.0	
			N=57		N=71	
Post-natal 6 months	Anaemia/Jaundice	0	0.0	3	4.2	0.1127
	Lymphadenopathy	2	3.4	2	2.8	0.8395
	CVS	0	0.0	1	1.4	0.3635
	GIT				N=70	
		0	0.0	1	1.4	0.4300
	UG	0	0.0	0	0.0	
	CNS	0	0.0	1	1.4	0.3635
	ENT	1	1.7	1	1.4	0.8870
	Skin	0	0.0	3	2.8	0.1127
	Respiratory	0	0.0	1	1.4	0.3635
			N=56		N=62	
Post-natal 9 months	Anaemia/Jaundice		N=55		N=61	
		0	0.0	1	1.6	0.3405
	Lymphadenopathy	1	1.8	0	0.0	0.2907
	CVS				N=61	
		0	0.0	0	0.0	
	GIT		N=55		N=61	
		0	0.0	1	1.6	0.3404
	UG	0	0.0	0	0.0	
	CNS				N=61	
		0	0.0	0	0.0	
	ENT	0	0.0	1	1.6	0.3395
	Skin	2	3.7	5	8.1	0.3935
	Respiratory	1	1.8	0	0.0	0.2907
			N=50		N=62	
Post-natal 12 months	Anaemia/Jaundice	1	2.0	0	0.0	0.2633
	Lymphadenopathy	3	6.0	0	0.0	0.0506
	CVS	1	2.0	0	0.0	0.2633
	GIT	1	2.0	0	0.0	0.2633
	UG	0	0.0	0	0.0	
	CNS	0	0.0	1	1.6	0.3670

	ENT	0	0.0	0	0.0	
	Skin	4	8.0	0	0.0	0.0223
	Respiratory	1	2.0	0	0.0	0.2633
			N=48		**N=56**	
Post-natal 15 months	Anaemia/Jaundice	0	0.0	1	1.8	0.3522
	Lymphadenopathy	0	0.0	0	0.0	
	CVS				**N=55**	
		0	0.0	1	1.8	0.3479
	GIT		**N=47**			
		0	0.0	0	0.0	
	UG				**N=54**	
		0	0.0	0	0.0	
	CNS		**N=47**		**N=47**	
		0	0.0	0	0.0	
	ENT	0	0.0	1	1.8	0.3522
	Skin	2	4.2	3	5.4	0.7772
	Respiratory	0	0.0	1	1.8	0.3522
			N=41		**N=48**	
Post-natal 18 months	Anaemia/Jaundice				**N=49**	
		0	0.0	3	6.1	0.1071
	Lymphadenopathy	1	2.4	0	0.0	0.2765
	CVS	0	0.0	1	2.1	0.3527
	GIT	0	0.0	0	0.0	
	UG	0	0.0	0	0.0	
	CNS		**N=40**			
		0	0.0	0	0.0	
	ENT	0	0.0	0	0.0	
	Skin				**N=49**	
		0	0.0	4	8.2	0.0993
	Respiratory	0	0.0	0	0.0	

APPENDIX 27

Abnormalities on physical examination for all the infants in ITT population who attended the visit

Visit	Variable	Vitamin A	N=50	Placebo	N=50	P-value
		n	%	n	%	
Post-natal 1 month	General appearance		N=49			
		1	2.0	0	0.0	0.3100
	Skin	4	8.0	3	6.0	0.6951
	Eyes				N=49	
		0	0.0	0	0.0	
	Musculoskeletal	0	0.0	0	0.0	
	ENT		N=49		N=48	
		2	4.1	1	2.1	0.5698
			N=62		N=74	
Post-natal 3 months	General appearance	5	8.1	5	6.7	0.7542
	Kin	5	8.1	7	9.5	0.7751
	Eyes	1	1.6	1	1.4	0.8996
	Musculoskeletal	0	0.0	0	0.0	
	ENT	4	6.5	6	8.1	0.5170
			N=56		N=69	
Post-natal 6 months	General appearance	9	16.1	7	10.1	0.3240
	Kin	6	10.7	7	10.1	0.9174
	Eyes	1	1.8	0	0.0	0.2651
	Musculoskeletal	0	0.0	0	0.0	
	ENT	5	8.9	6	8.7	0.9635
			N=54		N=62	
Post-natal 9 months	General appearance		N=53			
		4	7.5	5	8.1	0.9180
	Kin	4	7.4	6	9.7	0.6639
	Eyes	0	0.0	0	0.0	
	Musculoskeletal	0	0.0	0	0.0	
	ENT		N=53			
		2	3.8	5	8.1	0.3374
			N=49		N=59	
Post-natal 12 months	General appearance		N=50			
		6	12.0	7	11.9	0.9826
	Kin				N=60	
		3	6.1	7	11.7	0.3185
	Eyes	2	4.1	0	0.0	0.1173
	Musculoskeletal	0	0.0	0	0.0	
	ENT	6	12.2	5	8.5	0.5190
			N=48		N=55	
Post-natal 15 months	General appearance	5	10.4	3	3.5	0.3479
	Kin	7	14.6	0	0.0	0.0068
	Eyes		N=47			
		1	2.1	1	1.8	0.9105
	Musculoskeletal	1	2.1	0	0.0	0.2821
	ENT	2	4.2	2	3.6	0.8895
			N=41		N=49	
Post-natal 18 months	General appearance	4	9.8	2	4.1	0.2825
	Kin	6	14.7	4	8.2	0.3306
	Eyes	0	0.0	1	2.0	0.3576
	Musculoskeletal	1	2.4	0	0.0	0.2716
	ENT	1	2.4	4	8.2	0.2377

APPENDIX 28

The vital signs for all the mothers in ITT population who attended the visit

Visit	Variable[unit]	Statistic	Vitamin A	Placebo	P-value
Post-natal 1 months	Systolic blood pressure[mmHg]	N	50	50	
		Mean	121.2	122.5	0.6371
		SD	12.7	14.7	
		Min	90.0	100.0	
		Median	120.0	120.0	
		Max	160.0	190.0	
	Diastolic blood pressure[mmHg]	N	50	50	
		Mean	79.9	79.9	1.0000
		SD	1.0	11.3	
		Min	60.0	60.0	
		Median	80.0	80.0	
		Max	110.0	130.0	
	Heart rate[beats/min]	N	49	49	
		Mean	75.9	74.3	0.1792
		SD	6.6	4.8	
		Min	62.0	65.0	
		Median	76.0	75.0	
		Max	102.0	90.0	
Post-natal 3 months	Systolic blood pressure[mmHg]	N	64	74	
		Mean	119.0	120.9	0.4368
		SD	6.6	9.3	
		Min	95.0	100.0	
		Median	120.0	120.0	
		Max	140.0	160.0	
	Diastolic blood pressure[mmHg]	N	64	74	
		Mean	79.0	79.5	0.6703
		SD	6.1	6.9	
		Min	60.0	60.0	
		Median	80.0	80.0	
		Max	95.0	100.0	
	Heart rate[beats/min]	N	64	74	
		Mean	75.1	79.5	0.8239
		SD	3.5	6.9	
		Min	66.0	60.0	
		Median	76.0	80.0	
		Max	84.0	100.0	
Post-natal 6 months	Systolic blood pressure[mmHg]	N	57	70	
		Mean	120.5	119.8	0.6339
		SD	7.7	9.7	
		Min	110.0	100.0	
		Median	120.0	120.0	
		Max	155.0	160.0	
	Diastolic blood pressure[mmHg]	N	57	69	
		Mean	78.9	78.2	0.4514
		SD	6.5	6.1	
		Min	60.0	60.0	
		Median	80.0	80.0	
		Max	98.0	100.0	
	Heart rate[beats/min]	N	56	70	
		Mean	75.5	75.9	0.8453
		SD	3.6	4.8	
		Min	66.0	62.0	
		Median	76.0	76.0	
		Max	84.0	84.0	
Post-natal 9 months	Systolic blood pressure[mmHg]	N	56	61	
		Mean	118.4	118.4	0.9799
		SD	5.9	7.7	
		Min	110.0	100.0	
		Median	120.0	120.0	
		Max	135.0	140.0	
	Diastolic blood pressure[mmHg]	N	56	61	
		Mean	78.1	77.5	0.4558
		SD	4.5	5.1	
		Min	70.0	60.0	

		Median	80.0	80.0	
		Max	90.0	90.0	
	Heart rate[beats/min]	N	55	60	
		Mean	76.0	76.9	0.3471
		SD	5.2	7.5	
		Min	65.0	60.0	
		Median	76.0	76.0	
		Max	88.0	120.0	
Post-natal 12 months	Systolic blood pressure[mmHg]	N	51	63	
		Mean	115.4	117.0	0.4337
		SD	8.4	12.5	
		Min	100.0	100.0	
		Median	110.0	120.0	
		Max	150.0	200.0	
	Diastolic blood pressure[mmHg]	N	51	63	
		Mean	78.1	77.1	
		SD	4.7	7.6	0.4057
		Min	70.0	50.0	
		Median	80.0	80.0	
		Max	90.0	120.0	
	Heart rate[beats/min]	N	51	63	
		Mean	77.6	78.9	0.2878
		SD	7.1	5.3	
		Min	62.0	66.0	
		Median	76.0	76.0	
		Max	110.0	100.0	
Post-natal 15 months	Systolic blood pressure[mmHg]	N	48	57	
		Mean	114.7	115.5	0.4641
		SD	6.3	5.1	
		Min	100.0	110.0	
		Median	110.0	120.0	
		Max	135.0	125.0	
	Diastolic blood pressure[mmHg]	N	48	57	
		Mean	77.1	77.8	0.3471
		SD	4.1	3.6	
		Min	70.0	70.0	
		Median	80.0	80.0	
		Max	85.0	85.0	
	Heart rate[beats/min]	N	48	57	
		Mean	78.7	80.2	0.3396
		SD	4.7	9.6	
		Min	70.0	62.0	
		Median	76.0	78.0	
		Max	86.0	140.0	
Post-natal 18 months	Systolic blood pressure[mmHg]	N	41	49	
		Mean	113.4	114.4	0.5150
		SD	6.6	7.4	
		Min	100.0	100.0	
		Median	110.0	110.0	
		Max	140.0	140.0	
	Diastolic blood pressure[mmHg]	N	41	49	
		Mean	76.6	75.9	0.5553
		SD	4.5	6.5	
		Min	60.0	60.0	
		Median	75.0	75.0	
		Max	88.0	95.0	
	Heart rate[beats/min]	N	41	49	
		Mean	79.6	81.4	0.2162
		SD	6.8	7.0	
		Min	58.0	68.0	
		Median	84.0	84.0	
		Max	90.0	110.0	