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OBSTETRIC COMPLICATIONS IN MATERNAL DEATHS RELATED TO AIDS

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of

Master of Medicine in the branch of Obstetrics and Gynaecology

Johannesburg, 2007

DECLARATION

I, Berna Venter, declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in the branch of Obstetrics and Gynecology in the University of the Witwatersrand, Johannesburg. It has also been submitted to the College of Medicine in partial requirement for the qualification of Fellowship of the College of Obstetrics and Gynecology.

Berna Venter

Thirty first day of July 2007

DEDICATION

To my husband Dawie, my son Francois, who sacrificed so many hours of family time to allow me to finish this degree.

To my mother Carina and father Sybrand, who provided me with advice and prayed for me.

To brother Nic and sister-in-law Anelize, who listened to all my moans and groans.

To God, who carried me every step of the way.

PUBLICATIONS AND PRESENTATIONS ARISING FROM THIS STUDY

Sixteen years of maternal deaths related to HIV at Chris Hani Baragwanath Hospital. Proceedings of Ethicon conference; 15th September 2006; University of the Free State; Bloemfontein.

ABSTRACT

Objectives: To determine what obstetric complications can be associated with end-stage AIDS and maternal death.

Method: From 1990 to 2005 the maternal death files of patients with either AIDS-defining illnesses or CD4 counts of less than $200x10^6/\ell$ were analyzed in a descriptive study. All patients died undelivered or within 42 days of delivery.

Result: Sixty six percent (49/74) of pregnancies ended prematurely by preterm delivery or miscarriage. Twenty perinatal deaths occurred. The average birth weight was 1498g at an average gestational age of 30.5 weeks. The mean CD4 count was $45.5x10^6/\ell$. The majority of maternal deaths were caused by respiratory illnesses.

Conclusion: Preterm labour and early pregnancy loss are common among terminally ill pregnant women with AIDS. It is proposed that hypoxia in the presence of respiratory disease could lead to cytokine production in the uterine cavity, leading to preterm delivery, even in the absence of intrauterine infection.

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1) Professor EJ Buchmann, for supervising this research report.
2) Dr Manning, CEO of Chris Hani Baragwanath Hospital, for granting permission to conduct this research at the hospital.
3) The University of Witwatersrand Human Research Ethics Committee for approving the research from an ethical point of view.
4) Sybrand Bronkhorst, my father, who spent many hours reading through the report and giving advice on the lay-out of the paper.

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1. Introduction

With increasing prevalence of the Human Immunodeficiency Virus (HIV) infection in the general population of South Africa, it is only natural that acquired immunodeficiency syndrome (AIDS) related disease is becoming more common in the hospital environment. This is also true for the maternity hospital. The World Health Organization (WHO) figures indicate that the majority of the world's HIV positive population can be found in sub-Saharan Africa. By 2000, over 33.6 million people worldwide were estimated to be infected with HIV and an estimated 23.3 million of them were living in sub-Saharan Africa (over 50%) [1]. South Africa in particular is faced with an increasing number of HIV positive women and HIV positive pregnant women [1].

The South African Confidential Enquiries into Maternal Deaths of 1999-2001, found AIDS to be the leading cause of maternal death in South Africa [2]. In the more recent Saving Mothers Report (2002 – 2004) [3], it was reported that the four main causes of maternal death from 2002 to 2004 in the category of non-pregnancy related infection were AIDS (20.1%), pneumonia (9.6%), tuberculosis (3.2%) and meningitis (2.4%).

Recently, in South Africa, a programme has been launched to provide HIV positive patients with antiretroviral drugs. This programme may improve general

health of infected patients, as well as prolong their lives. This again, might cause a decrease in AIDS-related maternal deaths.

Infection with HIV may result in a spectrum of diseases, many of them poorly understood. It therefore becomes difficult to identify which complications during pregnancy should be attributed to the virus and which not. In the early stages of the disease, the pregnant patient is virtually unaffected and perinatal outcomes are comparable with the general population [4].

Medical staff at Chris Hani Baragwanath Hospital have observed that end-stage AIDS is associated with certain obstetric complications. A frequent occurrence is that a dying HIV positive mother presents with spontaneous preterm labour and gives birth to a small, often dead fetus, before she herself passes on. The mechanism for this is unclear, but may be related to severe infection with production and circulation of cytokines which induce labour [5].

The objective of this study was to establish whether there is a trend towards certain obstetric complications among terminally ill pregnant patients with AIDS and to see whether there is an association between their AIDS-related conditions and the obstetric complications. The obstetric outcomes of interest were intrauterine fetal death and spontaneous preterm labour. This study may help to improve understanding of illness and mortality.

2. Literature review

In the sections to follow, literature will be discussed as a prelude to the findings of the study. Special attention will be paid to AIDS and HIV infection, as well as management of the epidemic in the South African setting.

2.1 Preterm labour

It has been suggested that preterm labour occurs secondary to infection of the amniotic fluid, membranes and placenta. This may associated with HIV infection. At the United Arab Emirates Government Hospital in Manipur, India, 153 placentas were preserved in formalin and samples taken from the membranes as well, after postpartum expulsion. The specimens were processed and stained with haematoxylin-eosin. The sections were then examined for histological evidence of inflammation. It was found that placental membrane infection was more frequent among HIV positive women and highest among those who delivered preterm [6].

It has also been suggested that the AIDS disease process somehow leads to an increase in cytokine levels in the amniotic fluid, which in turn induces preterm contractions. In a study conducted by Figueroa, et al. [7], amniocentesis was performed on 52 women with preterm labour and intact membranes. The fluid was cultured and tested for interleukins with sensitive and specific enzyme-linked immunosorbent assays (Table 1).

<u>TABLE 1</u> – Summary of the results of the study of Figueroa, et al. [7] on the relevance of intra-amniotic cytokine levels to preterm labour.

	Delivered within 7 days of amniocentesis		**Undelivered 7 days after amniocentesis**	
Women (N=52)	32 (62%)		20 (38%)	
Amniotic fluid cultures	**Positive**	**Negative**	**Positive**	**Negative**
	9 (28%)	23 (72%)	0 (0%)	20 (100%)
Cytokine levels	Very high	High	Low	Low

Sixty two percent of women delivered within seven days of amniocentesis and of those, 28% had positive cultures. Those that delivered within seven days had significantly higher levels of interleukin-1alpha, interleukin-6 and interleukin-8 than the women who delivered after seven days, regardless of culture results. Cytokine levels were higher among women who had positive amniotic fluid cultures than those who had negative cultures, but as a group their levels were higher than the women who delivered after seven days.

Another study, also from the USA, found a similar association between elevated cord and/or placental interleukin-6 and interleukin-8, and preterm delivery and chorioamnionitis [8].

Bodkin, et al. [4] conducted a study at a public sector hospital in Johannesburg, to compare maternal and fetal outcomes between HIV positive and HIV negative

women. Among their findings was the significant likelihood that HIV positive women had a greater chance of having intrauterine fetal growth restriction, earlier delivery and smaller babies than HIV negative women. The average gestational age at birth for the HIV positive women in their study was 37.92 weeks. This value does not represent preterm delivery as such, but was significantly lower than the 38.5 weeks for the HIV negative group (37.9 vs. 38.5 weeks, P=0.03).

2.2 Spontaneous miscarriage

It has been debated for some time whether HIV infection has an effect on fetal wastage. In some studies this finding was confirmed. At the Baylor College of Medicine it was found that miscarriage was three times more likely among HIV-infected women than their HIV-uninfected counterparts [9]. The typical rate quoted in this publication for non-HIV-infected women was less than three percent (for second trimester miscarriages). One hundred and twenty four HIV-infected women were studied and more than 11% had miscarried in the second trimester. Four possible causes listed for this finding of increased risk of spontaneous miscarriage among HIV-infected women were: HIV toxicity to the fetus, fetal thymic dysfunction, placental changes and elevated uterine levels of interleukin-4, interleukin-6 and tumour necrosis factor [9].

In Nairobi, in a case control study, 13.8% HIV-infected women suffered spontaneous miscarriage versus 6.2% of HIV-uninfected women. This indicates

that HIV infection was significantly associated with a higher incidence of spontaneous miscarriage (p=0.02) [10].

Several other studies have found similar trends among HIV-infected women, which bring to mind the question as to exactly what causes these trends. HIV and AIDS obviously have far-reaching effects that are poorly understood and need further investigation.

2.3 Fetal outcome

As seen in studies in other parts of the world, fetal outcome worsens as HIV infection progresses to AIDS and the condition of the mother deteriorates.

It is evident that HIV infection has real implications for the fetus of the HIV positive mother. A systematic review and meta-analysis of 31 studies was done by Brocklehurst and French in Oxford, in the UK [11]. The authors found an association between maternal HIV infection and adverse neonatal outcome, although the association was not strong. It also appeared that the association was stronger for studies done in developing countries such as Kenya, India and Pakistan. The adverse outcomes included spontaneous miscarriage, stillbirth, fetal abnormality, perinatal death, neonatal death, infant death, intrauterine growth restriction, low birth weight and preterm delivery.

In a study done in Zaire, a similar picture emerged. The neonatal death rate in infants of seropositive mothers was considerably higher than in the group of infants born to seronegative women [12].

South Africa, like many countries in the world, has a policy of providing antiretroviral drugs to pregnant HIV positive mothers, in an attempt to at least prevent the infants from being infected with HIV, even if the mother cannot be cured.

More or less a third of babies born to HIV-infected mothers, irrespective of maternal health and gestation, will also be infected with HIV if no preventative measures are taken [13]. It is thought that most infections occur in the intrapartum period and that a further set of infants contract the virus through breastfeeding. It has been established that a trustworthy predictor of transmission from mother to fetus is viral load, which in turn is a reflection of maternal health. Modified obstetric practices, like delay of rupture of membranes, elective caesarean section and vaginal cleansing, may reduce the risk of vertical transmission of HIV, but antiretroviral treatment is proven to have the greatest effect in this regard [13].

Nevirapine, a non-nucleoside reverse transcriptase inhibitor, is widely used in South Africa. Mothers in labour take a single dose of 200 mg approximately six hours before the expected time of delivery and the neonate is also given a single

dose of 2 mg/kg body weight within 24 to 72 hours of delivery. This regimen has been shown to reduce intrapartum vertical transmission by up to 47% [14].

2.4 Maternal outcome

It seems that the pregnant state, in turn, has a detrimental effect on the health of the HIV-infected mother and indeed speeds up the progress of the disease.

From 1992 to 1996 Kumar, et al. [5] recruited 71 tribal women from Manipur, India. Of these, 32 were pregnant, the others not. The subjects were matched for age, parity, CD4 lymphocyte count and demographic characteristics. The women all had AIDS, stage three or four (WHO clinical staging of HIV disease, Table 3) [15]. In the pregnant group, 15 patients contracted Pneumocystis jeroveci pneumonia (PCP), of whom 12 died. Three patients died soon after medical termination of pregnancy, seven in the third trimester of pregnancy, and two in the immediate postpartum period. In the non-pregnant group four patients died of PCP. In the pregnant group six more patients died undelivered – five from tuberculosis and one from wasting syndrome. In total, 18 of the pregnant patients passed away within 17 months of falling pregnant. Fourteen patients delivered preterm. Eleven of the premature infants died within six weeks of birth. Prematurity and the clinical diagnosis of an AIDS-defining illness was the cause of death in nine of these infants. Only 10 of the 39 non-pregnant patients died during the course of the study. The 29 surviving non-pregnant patients seemed reasonably well at the end of the study (at 42 months follow up). The mean

survival time, from the start of the study, for the pregnant mothers who died was 9.72 months and for the non-pregnant group 22.6 months. This study showed that not only does maternal and fetal outcome deteriorate as the disease progresses, but also that pregnancy has a considerable influence on the course of the disease.

A systematic review of the literature and meta-analysis done by French and Brocklehurst [16], investigated the effect of pregnancy on disease progression and survival in woman infected with HIV (Table 2).

The women in the review were all pregnant and were compared to a control group of women infected with HIV that were not pregnant. Seven studies were included in the review. The results showed that pregnant HIV-infected women were more likely to experience some deterioration in the HIV disease, progress to have an AIDS defining illness, die, or their CD4 count decrease below 200 **x** $10^6/\ell$ than HIV-infected women that were not pregnant. These findings only show a trend, as most of the associations were not statistically significant. This trend was shown to be more pronounced in developing countries. The statistics follow in Table 2.

As seen in these two papers, especially in advanced HIV disease, pregnancy can have an adverse effect. This effect depends on the stage of the disease at the onset of the pregnancy and can vary from progression to AIDS to death.

***TABLE 2* – Summary of results of the review and meta-analysis done by French and Brocklehurst [16].**

Adverse maternal outcome related to HIV infection and pregnancy	Summary odds ratio	Confidence interval
Death	1.8	85%; 0.99 – 3.3
HIV disease progression	1.41	95%; 0.85 – 2.33
Progression to AIDS-defining illness	1.63	95%; 1.00 – 2.67
Fall of CD4 count to below 200 x 10^6/ℓ	0.73	95%; 0.17 – 3.06

In New York, USA, it was found that PCP is the most common cause of AIDS-related death in pregnant women in the United States. Ahmad, et al. [17] reviewed 22 cases of patients with PCP in pregnancy. Thirteen patients developed respiratory failure and had to be mechanically ventilated. Of the ventilated patients only 31% survived. The overall mortality rate was 50%. This rate is much higher than those quoted for the general HIV positive population for PCP mortality. The conclusion was that PCP has a more aggressive course in pregnancy with poor maternal and fetal outcomes [17].

In Africa, tuberculosis is probably the most common opportunistic infection among HIV-infected patients. As the CD4 count falls, the risk of tuberculosis increases. However, tuberculosis can occur at any level of CD4 count. In 2000, it

was estimated that 50% of patients with tuberculosis in South Africa were also HIV positive [18]. Tuberculosis in HIV positive patients is difficult to diagnose, because the acid-fast bacilli smears are frequently negative and extra-pulmonary tuberculosis is more common. Tuberculous meningitis is seen more often. If a patient presents with pulmonary tuberculosis, the shift is away from the classical apical, cavitating presentation, towards a more widespread non-specific mid- and lower-zone infiltrate that mimics other conditions such as community acquired pneumonia and PCP [18].

The fact that tuberculosis presents more commonly as an opportunistic infection in the HIV-infected mother, has also been observed in a study in Lusaka, Zambia. In 1996 and 1997, 251 maternal deaths were recorded at the University Teaching Hospital in Lusaka. The different causes of deaths were as follows:

1) Direct causes (Obstetric causes) 106 (42%)
2) Indirect Causes (Non-obstetric causes) 145 (58%)
    - Malaria 30%
    - Tuberculosis 25%
    - Unspecified chronic respiratory tract infections 22%

Ninety two percent of the patients who died of tuberculosis were also HIV-infected, as well as 97% of the patients that died of unspecified chronic respiratory tract infections. The maternal mortality ratio at this hospital increased from 118/100 000 live births in 1982 to 921/100 000 in 1997. The author of this

publication stated that urgent attention should be paid to the timely diagnosis of AIDS-related tuberculosis in pregnancy [19].

2.5 AIDS – acquired immunodeficiency syndrome

The face of medicine has changed considerably with the emergence of HIV and AIDS, and related diseases. It is sometimes difficult to recognise the different ways the disease can present itself. Therefore, the World Health Organisation has created a clinical classification system to facilitate management of HIV positive patients [15].

With the use of this classification system, it is easy to establish in which stage of the disease the patient is, and which treatment to start. This system is also of use in managing the antiretroviral treatment rollout programme that was initiated by the SA Government on 8 August 2003 [20].

The following tables are directly quoted from the WHO Case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children (2006) [15].

<u>TABLE 3</u> - Clinical staging of HIV disease (World Health Organization – 2006)

CLINICAL STAGE 1
Asymptomatic **Persistent generalised lymphadenopathy**
CLINICAL STAGE 2
Unexplained moderate weight loss (<10% of presumed / measured body weight) **Recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media, pharyngitis)** **Herpes zoster** **Angular cheilitis** **Recurrent oral ulceration** **Papular pruritic eruptions** **Seborrhoeic dermatitis** **Fungal nail infections**
CLINICAL STAGE 3
Unexplained severe weight loss(>10% of presumed / measured body weight) **Unexplained chronic diarrhoea for longer than one month** **Unexplained persistent fever (above 37.5˚C intermittent or constant, for longer than one month)** **Persistent oral candidiasis** **Oral hairy leukoplakia** **Pulmonary tuberculosis** **Severe bacterial infections (such as pneumonia, empyema, pyomyositis, bone or joint infection, meningitis or bacteraemia)** **Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis** **Unexplained anaemia (<8g/dℓ), neutropaenia (<0.5 x 10^9/ℓ) and/or chronic thrombocytopenia (<50 x 10^9/ℓ)**

CLINICAL STAGE 4
HIV wasting syndrome
Pneumocystis pneumonia (PCP)
Recurrent severe bacterial pneumonia
Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month's duration or visceral at any site)
Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
Extrapulmonary tuberculosis
Kaposi's sarcoma
Cytomegalovirus infection (retinitis or infection of other organs)
Central nervous system toxoplasmosis
HIV encephalopathy
Extrapulmonary cryptococcosis including meningitis
Disseminated non-tuberculous mycobacterial infection
Progressive multifocal leukoencephalopathy
Chronic cryptosporidiosis
Chronic isosporiasis
Disseminated mycosis (extrapulmonary histoplasmosis or coccidiomycosis)
Recurrent septicaemia (including non-typhoidal *Salmonella*)
Lymphoma (cerebral or B-cell non-Hodgkin)
Invasive cervical carcinoma
Atypical disseminated leishmaniasis
Symptomatic HIV-associated nephropathy or symptomatic HIV-associated cardiomyopathy

2.6 Antiretroviral treatment for preservation of general health in HIV-infected patients

As it is now policy in many countries in the world to provide antiretroviral treatment to AIDS sufferers, the question still remains when and how to start this treatment.

Severe, et al. [21] conducted a study in Haiti on 1004 HIV-infected patients with a median CD4 count of 131 x $10^6/\ell$. Three drugs were used. The patients were followed up for 14 months and according to a Kaplan-Meier analysis 87% of adults were still alive at the end of the period. After 12 months, the median increase in CD4 count was 163 x $10^6/\ell$. A decrease in viral load was also demonstrated [21]. In the last mentioned study, the findings indicated an improvement in the condition of the subjects on treatment.

However, in other studies it has been demonstrated that initiation of treatment after the CD4 count has fallen below 200 x $10^6/\ell$, results in worse outcomes than when treatment is started at a higher count. At Montefiore Medical Centre and Lincoln Medical and Mental Health Centre in Bronx, New York, USA [22], 1054 HIV-infected women were recruited in a study to determine the time interval from initiation of highly active antiretroviral treatment to development of AIDS and death.

<u>TABLE 4</u>– Results for the study of Anastos, et al. [22], summarised

CD4 Counts (x $10^6/\ell$)	Relative hazards for progression to AIDS	Confidence interval (95%)	Relative hazards for progression to death	Confidence interval
200 – 350	0.92	0.46-1.86	1.97	0.84-4.66
< 200	2.48	1.39-4.42	3.35	1.59-7.08

As seen in Table 4, women with lower CD4 counts at initiation of antiretroviral treatment had a much higher risk of developing AIDS and dying, as compared with women with higher CD4 counts (more than 350 x $10^6/\ell$). Also, the lower the CD4 count at initiation of treatment, the higher the risk of progression to death [22].

3. Subjects and methods

This was a retrospective descriptive study. The Maternity unit at Chris Hani Baragwanath Hospital in Soweto, Gauteng, South Africa, was chosen for the site of this study. The maternal death files for the years 1990 to 2005 were kept separate from the usual record stores and were easy to locate for research purposes.

All files of patients that had evidence of AIDS, as defined by a CD4 count below 200 x $10^6/\ell$ or an AIDS-defining illness that died undelivered or within 42 days of delivery or miscarriage, were included in the study. A data sheet was compiled to collect information from the files. This data sheet is attached as Appendix A. Information such as parity, gravidity, gestational age at delivery, cause of death, birth weight of the neonate and antenatal history were extracted from the files. The data was summarised by means of tabulation, analysed and then interpreted to reach a rational conclusion.

The statistical method used, was descriptive including calculation of totals by addition of figures, calculation of frequencies, with percentages, means with standard deviations, and medians with ranges. Calculations and tabulations were done using Microsoft Excel software.

Prior to the commencement of the study, approval to perform the study was granted by the Chief Executive Officer of Chris Hani Baragwanath Hospital and the University of Witwatersrand Human Research Ethics Committee [Appendix B].

4. Definitions

The following fundamental terminology was used throughout the paper and some clarity on the precise meaning of each phrase is necessary.

4.1 Maternal death

A maternal death is defined as the death of a woman while pregnant or within 42 days after delivery, miscarriage, termination or other loss of a pregnancy.

4.2 AIDS – acquired immunodeficiency syndrome

In this study, for a patient to be classified as having 'AIDS-related complications' there would have to be:

1) A positive HIV result

   AND

2) The presence of an AIDS-defining illness (WHO Classification, Stage IV, refer section 2.5)

   OR

   A CD4 count of less than 200 x $10^6/\ell$. (Refer section 4.8)

4.3 Preterm labour

Preterm labour is defined as the onset of true labour - painful contractions accompanied by cervical changes - before the gestational age of 37 completed weeks [23].

4.4 Term pregnancy

A term pregnancy is a pregnancy that proceeds to between 37 completed and 42 weeks of gestation. A fully developed and normal neonate should be the product of such a pregnancy.

4.5 Viable pregnancy

In this study, a viable pregnancy was considered as a gestation of 26 completed weeks and more or a fetal birth weight of 900 g and more. This definition is used, because some neonatal units in the public sector in South Africa use these values as cut-off points for qualification for ventilation in neonatal intensive care units. Financial and technological constraints result in this limitation on the size of babies these units are able to manage.

4.6 Low birth weight

Low birth weight is considered as a birth weight less than 2500 g, regardless of the gestational age [24].

4.7 Intrauterine growth restriction

Intrauterine growth restriction is diagnosed when the fetal birth weight is below the tenth percentile for gestational age in weeks or abnormal growth parameters are found on detailed ultrasound scan [24].

4.8 Helper T-lymphocytes (CD4 count)

The CD4 count is the number of helper T-lymphocytes in a cubic millimetre of blood. As HIV infection progress, the CD4 count decreases, and when it falls below 200 x $10^6/\ell$, the disease is in the AIDS phase. The normal value is around 1000 x $10^6/\ell$. A T-lymphocyte is a subtype of leucocyte (white blood cell) [24]. Hereafter helper T-lymphocytes levels in this paper will be referred to as CD4 counts.

4.9 *Pneumocystis jiroveci* pneumonia (PCP)

Pneumocystis carinii pneumonia is commonly referred to as PCP in the medical realm. It is noted that the causal organism underwent a name change recently from *Pneumocystis carinii* to *Pneumocystis jiroveci* to give

credit to the scientist who discovered the organism. The organism will be named accordingly in this paper, but for the sake of consistency the disease caused by the organism will, for the remainder of the paper, be referred to as PCP [25].

4.10 Delivered and undelivered

Patients whose babies were born before the time of death will be referred to as ‘delivered’ and those patients whose babies were not born before the time of death, thus dying in utero, will be referred to as ‘undelivered’.

4.11 Neonate and neonatal period

A neonate is the term used for a newborn baby in the first 28 days of life, hence, the neonatal period is also the first 28 days of life. The early neonatal period refers to the first 7 days of life [23].

4.12 Synonyms for an HIV positive result

In this paper several synonyms are used all indicating a positive HIV serology test: HIV-infected, HIV reactive, seropositive, HIV positive.

5. Results

5.1 Study subjects

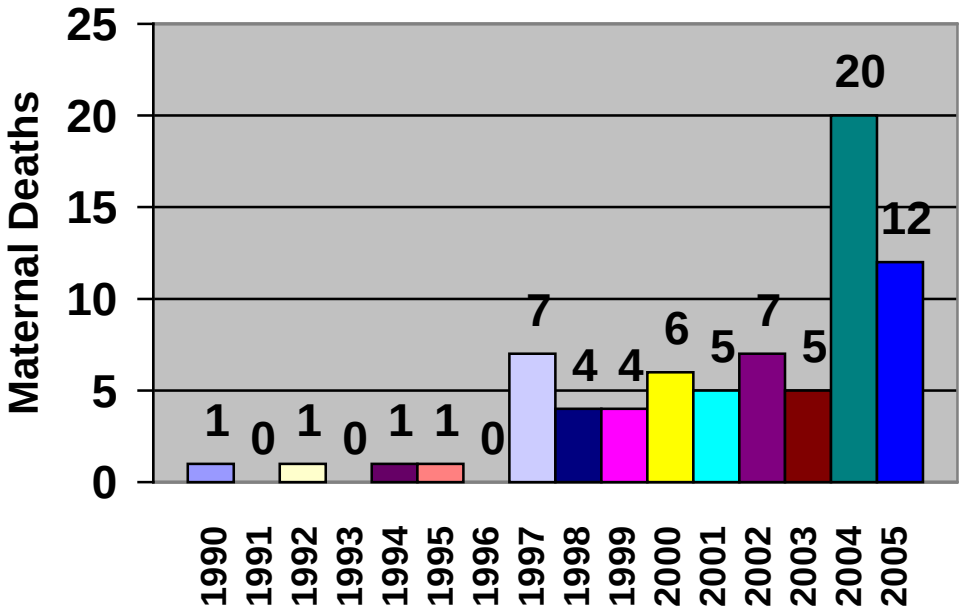


***FIGURE 1* – Bar chart showing HIV-related maternal deaths per year at Chris Hani Baragwanath Hospital from 1990 to 2005.**

The files of 74 patients were found. The dates of HIV-related maternal deaths range between January 1990 and December 2005. The mean age at death was 28.2 years, with the youngest patient 18 years of age and the oldest 40 years old. The national prevalence of HIV infection in 1990 was estimated at 0.8% from the attendance of antenatal clinics by national survey. This had increased by the

end of 2000 to 24.9% [26]. The results obtained in this study are therefore in keeping with the national figures of increase in HIV infection and ultimately HIV-related deaths as seen by the increase in numbers of deaths in the later years in this study.

5.2 CD4 counts and antenatal history of the research subjects

All patients included in the study were recorded to have a reactive HIV test. It is not compulsory to have an HIV test at an antenatal clinic, but it is offered to all mothers, together with counselling.

Regarding the status of HIV infection, the patients whose CD4 counts were available had low counts, the mean being 45.5 x $10^6/\ell$. Only 49 patients had a CD4 count available, despite lengthy hospitalisation periods. In a number of the cases that had no results, the test appeared to have been done, but the result could not be found. In earlier years, the test was rarely requested, probably because of lack of knowledge about HIV/AIDS or expense of the test at that time.

Fifty nine patients attended antenatal clinic and 15 patients did not. The mean number of antenatal visits was 4.01. The mean parity was 1.24 and the mean gravidity was 2.32. Syphilis serology testing revealed three infected and 50 uninfected patients, and 21 whose results were not available.

5.3 AIDS-related causes of deaths

The causes of deaths were diverse but a clear trend towards respiratory diseases was evident. (Table 5)

A large portion of the study subjects, 55 (74.3%), died of respiratory causes directly linked to their HIV status. This number consists of three contributors: PCP: 17 (23.0%), community-acquired pneumonia: 16 (21.6%) and pulmonary tuberculosis: 22 (29.7%). The second apparent group of causes were the central nervous system group at 15.0% (11), consisting of tuberculous meningitis: 5 (6.8%), cryptococcoma: 3 (4.1%) and bacterial meningitis: 3 (4.1%). Therefore, the respiratory and central nervous system causes together accounted for 89.2% (66/74) of the maternal deaths.

Patients were accepted into the PCP classification following documented therapeutic treatment for PCP, chest x-ray picture or clinical picture suggesting PCP. None of the patients had microbiological evidence of PCP, due to the difficulties in obtaining positive results from sputum, or doing bronchoscopic washings.

The diagnosis of cerebral cryptococcoma was made by computerised tomography scan and lumbar puncture. With meningitis, lumbar punctures were done and positive results for viral, bacterial or fungal meningitis were obtained. Patients classified as having ‘pneumonia’ had a lower respiratory infection, but

the infective organism was rarely identified. These patients most probably had some community acquired pneumonia, but might have had either PCP or tuberculosis.

TABLE 5 - Causes of death in HIV related maternal mortalities at Chris Hani Baragwanath Hospital from 1990 to 2005. (n=74)

Cause	Number	Percentage
Postpartum haemorrhage	1	1.4
Tuberculosis Meningitis	5	6.8
AIDS – wasting syndrome	2	2.7
PCP	17	23.0
Meningitis	3	4.1
Cryptococcoma	3	4.1
Pulmonary tuberculosis	22	29.7
Community-acquired Pneumonia	16	21.6
Puerperal sepsis	3	4.1
Malaria	1	1.4
Kaposi sarcoma	1	1.4

Three patients had postpartum sepsis (‘puerperal sepsis’) as cause of death and eventually one had a subtotal hysterectomy. Two more patients had postpartum sepsis as complication, but died of other causes (Table 6). One patient had been diagnosed with malaria, acquired in another African country. She had advanced AIDS and died undelivered.

5.4 Obstetric complications

There was a high incidence of preterm labour and miscarriages among the patients studied (Table 6). Most patients experienced more than one complication, with the result that the number of complications did not add up to 74. Each complication is separately reflected as a percentage of the patients who experienced the complication in relation to the total number of patients.

Forty three patients (58.1%) experienced spontaneous preterm labour. Some received tocolytic drugs, but eventually 39 patients delivered premature infants. Ten pregnancies (13.5%) ended in miscarriage.

A total of 49 (66.2%) pregnancies ended preterm. This figure is obviously significantly more than for the general population. From the data, there is no clear cause other than terminal illness and, in most cases, additional infection elsewhere in the body. Only one case of chorioamnionitis (1.4%) and four cases of preterm prelabour rupture of membranes (5.4%) were diagnosed. However, the clinicians did not make a specific search for chorioamnionitis in most of these pregnancies.

<u>TABLE 6</u> – Obstetric complications documented in HIV-related maternal deaths at Chris Hani Baragwanath Hospital from 1990 to 2005

Complication	Patients	Percentage
Preterm labour	43	58.1
Fetal distress	10	13.5
Intrauterine growth restriction	6	8.1
Intrauterine fetal death	6	8.1
Pre-eclampsia	2	2.7
Preterm prelabour rupture of membranes	3	4.0
Induction of labour	4	5.4
Postpartum sepsis	5	6.7
Retained products	9	12.1
Miscarriage	10	13.5
Breech presentation	3	4.0
Cephalopelvic disproportion	1	1.4
Assisted delivery	2	2.7
Sub/total hysterectomy	2	2.7
Hysterotomy	1	1.4
Placenta accreta	1	1.4
Chorioamnionitis	1	1.4
Anhydramnios	2	2.7
Thrombotic thrombocytopaenic purpura	1	1.4
Post-partum haemorrhage	4	5.4
Uterine scar dehiscence	1	1.4
Abruptio placentae	1	1.4

One case each of placenta accreta, thrombotic thrombocytopaenic purpura, chorioamnionitis, uterine scar dehiscence and abruptio placentae (1.4% each)

were documented. These four conditions are not thought to be related to HIV or AIDS.

Death followed on average 7.9 days after delivery, in those patients who gave birth.

<u>TABLE 7</u> – Mean CD4 counts for the major groups of obstetric complications

Condition	Number	Number with known CD4 count	Mean CD4 count ± SD
Preterm labour	43	29	47.3 ± 42.1
Miscarriage	10	6	34.5 ± 16.8
Obstetric infection	5	5	75.0 ± 73.0
Other obstetric complications	16	12	29.6 ± 21.4

In the preceding table it can be noted that the lowest mean CD4 counts were found in patients that suffered miscarriages and other obstetric complications. Due to the low numbers in this study, it is difficult to demonstrate a plausible trend.

Six fetuses (8.1%) were diagnosed with intrauterine growth restriction and six (8.1%) died in utero. Fetal distress was documented in 10 cases. Not all patients were in labour at the time of this finding and not all were medically fit for

caesarean section. Thus, in view of poor maternal condition in some cases, the fetus was allowed to die in utero in order to try and prolong the mother's life. Hence, a total of 22 fetuses (43.1% - 22/51 viable pregnancies) had some insult in the uterus.

5.5 Fetal outcome

Of the 74 patients studied, 13 died undelivered (17.6%), 10 had miscarriages (13.5%) and 51 delivered viable fetuses (68.9%). Fourteen babies were stillborn. Of 37 babies that were born alive, six died during the early neonatal period. Therefore, only 31 (60.8%) neonates of the possible 51 viable deliveries survived the early neonatal period. The 13 fetuses that were undelivered at the time of the death of the mother were all alive at the time of the simultaneous death. The average gestational age of these babies was 27.9 weeks.

***TABLE 8* – Comparison of fetal outcome associated with respiratory and other infections**

Outcome	Respiratory infections	Other infections
Undelivered (N=13)	8 (61.5%)	5 (38.5%)
Miscarriage (N=10)	10 (100%)	0 (0%)
Stillbirth (N=14)	9 (64.3%)	5 (35.7%)
Early neonatal death (N=6)	3 (50%)	3 (50%)
Preterm delivery (N=43)	28 (65.1%)	15 (34.9%)
Surviving infant (N=31)	21 (67.7)	10 (32.3%)

It should be noted that in all categories of fetal outcome, maternal respiratory disease was more prevalent than other infections.

The mean birth weight of neonates delivered was 1698 g, with the lowest weight 900 g and the highest 2950 g (among the viable fetuses). A total of 36 babies where the weight was known had a low birth weight. Only three neonates had a birth weight above 2500 g. In 13 babies the weight was unknown. The average gestational age at birth was 30.5 weeks. This very low figure has implications on the health system as premature infants need special care in order to survive, sometimes at considerable cost.

Fourteen deliveries were by caesarean section (27.5%). Two vaginal deliveries were assisted due to poor maternal health. There were two sets of twins, whose mothers both died undelivered. Sex was equally distributed among the neonates at 51% female and 49% male.

6. Discussion

The aim of the study was to identify a trend towards specific obstetric complications among terminally ill patients with AIDS. Preterm labour and early pregnancy losses were unusually common. In addition, fetal outcome was poor, with a high perinatal mortality rate.

6.1 Preterm labour

It has been suggested in the literature that preterm labour may occur secondary to intrauterine infection.

If it is true that preterm labour is most likely caused by chorioamnionitis, then the more advanced the stage of HIV infection, the greater the chances of having preterm labour. This suggests that a large proportion of these women may have chorioamnionitis, even if it was sub-clinical.

In this study, over half of these women experienced preterm birth. Considering the preceding discussion, it seems clear that women in the terminal stages of AIDS, with various associated infectious conditions, are at risk for preterm labour. The average CD4 count was 45.5 x $10^6/\ell$, predisposing these women to severe infections, most likely to cause cytokine release, in turn leading to uterine contractions, and preterm labour.

6.2 Spontaneous miscarriage

It was observed during the data collection for this paper that a high number of patients (10/74 - 13.5%) experienced spontaneous miscarriage. This number is higher than expected when compared to the general HIV negative population.

Many papers published also indicated a higher rate of miscarriages among the HIV positive subjects of their studies. It leaves the question whether HIV testing should be done routinely as investigation of the cause of miscarriage and not only in later pregnancy for the prevention of HIV transmission from mother to child.

The mechanism for the increased miscarriage rate among HIV-infected mothers is unclear. It could be that the same process that ends viable pregnancies prematurely, is responsible for miscarriage.

6.3 Fetal outcome

In this study, only 60.8% (31/51) of viable pregnancies resulted in a live infant past the first seven days of life.

A very large contributing factor to the unusually high perinatal mortality rate is the large group of preterm deliveries in this study group. Many infants died in the neonatal period due to prematurity. It could not be determined whether some of them died directly as a result of HIV infection. There was also a high stillbirth

rate. The exact cause of this could not directly be deduced from the information in the files, but if one considers the high incidence of fatal maternal respiratory disease, hypoxia could have played a role in the death of these fetuses.

The follow-up period for infants in this study was short due to the retrospective nature of the data collection and relatively poor record keeping in some of the files. It is therefore impossible to say what the long term outcome and in particular the incidence of transmission of HIV from mother to child was. The possible infant death rate in the study group could have been even higher if this information had been available.

The average gestational age at birth (30.5 weeks) and relatively low birth weights are in keeping with the findings of research done elsewhere. It could be said, however, that the more advanced the disease, the more likely preterm delivery and intrauterine growth restriction will be. Obviously, in view of the high incidence of prematurity in this group, the perinatal mortality rate would be much higher than in healthier patients where the mean gestational age at birth would be slightly higher.

In the calculation of the mean birth weight in the results of this paper, the number is artificially low, because so many preterm deliveries occurred. During the capturing of data, it was however noted that term neonates also often had low birth weights. This could be due to the general poor health of the mothers, poor

nutritional status, pathology in the placenta or some metabolic process in the body of the mother.

Another alarming finding was the frequent finding of fetal distress documented. Over 13% (10/74) of fetuses had distress with or without labour. Some babies could clearly not withstand the stress of labour and those that experienced distress out of labour apparently suffered some insult relating to maternal disease. They may have been hypoxic secondary to maternal disease, but this could not be validated due to the retrospective nature of the study.

6.4 Maternal outcome

Maternal outcome in this study was, by definition, dismal. As stated in the title of the paper, all subjects died. All patients were severely immuno-suppressed, as reflected by low CD4 count or the presence of an AIDS-defining illness. The maternal outcome in this research can evidently not be generalized, as these patients were selected for the fact that they died within 42 days of delivery or still being pregnant when they died. The trend towards certain causes of deaths is worthy of discussion.

In this study, 74.3% of study subjects died of pulmonary causes (Table 5). This is not surprising when a careful literature study is conducted, as similar findings have been reported elsewhere [17, 18, 19].

The other large group of mortalities (15%) could be assigned to central nervous system causes. This complication is common in patients with AIDS.

Pregnant patients are clearly at risk of contracting severe pulmonary or central nervous system infections. Aggressive prevention and treatment of these conditions should be a priority in pregnant patients with AIDS. Although co-trimoxazole and anti-TB treatment are routinely given to confirmed cases of PCP and tuberculosis, thought should be given to aggressive prevention with prophylactic doses of cotrimoxazole e.g. two tablets Bactrim daily. Clinicians should actively be on the look-out for respiratory and nervous system infection in HIV positive pregnant patients.

6.5 AIDS – acquired immunodeficiency syndrome

HIV infection is on the increase in South Africa. There is a noticeable increase in yearly incidence of AIDS-related maternal deaths with no deaths in some years in the early nineties, up to 20 deaths in 2004 (Figure 1). Thus, almost 2 patients per month died in 2004.

A lack of proper investigation of HIV positive patients was seen in the files of patients in the earlier years of the investigation. CD4 counts were not requested or the results were not obtained and documented in the files. This finding can indicate that the understanding of the disease in the early nineties was wanting, but improved in the years that followed. As more patients with HIV infection and

AIDS presented, clinicians became more experienced in managing these patients.

6.6 Antiretroviral treatment for preservation of general health in HIV-infected patients

With a study such as this demonstrating the need for effective treatment for general health and some improvement in life expectancy, the necessity of antiretroviral treatment is evident. Even though data is insufficient, studies like those conducted by Severe, et al. [21] and Anastos, et al. [22] have suggested improvement in CD4 counts and survival in patients with AIDS on antiretroviral drugs.

In South Africa, it is policy to start treatment at a CD4 count less than 200 x $10^6/\ell$. This may mean that patients in this country have a poorer prognosis because of delayed commencement of treatment. Consideration should be given to increasing the lower cut off of the CD4 count to 350 x $10^6/\ell$ to qualify for antiretroviral treatment [22]. As seen in this study and in research done elsewhere in the world, pregnancy speeds up the progress of AIDS. Therefore it should be investigated whether pregnant patients should perhaps start antiretroviral treatment at even higher CD4 count levels.

The study subjects had an extremely low mean CD4 count and considering the fact that all of them died in the peripartum period, one is concerned about

patients deteriorating to such poor health if treatment could prevent it. It seems that none of the patients of this study were on antiretroviral treatment as no such treatment was documented in the files. Therefore it is impossible to comment on the effect of such treatment in this particular study. It can only be speculated whether antiretroviral treatment, commenced in good time, could have prevented some of the deaths in this research project.

6.7 Placental interleukin release in response to hypoxia

Considering the association between preterm delivery and possible increased production of cytokines into the uterine cavity, one needs to investigate the possible mechanism of this increased production. Even though the raised cytokine levels are associated with infection, other possible mechanisms of increased production do exist.

An article by Malek, et al. [27] discusses placental hypoxia and ischaemia in pre-eclampsia. The effect of hypoxia, oxidative stress and lipopolysaccharides were determined on human term placental tissue explants. Prostaglandin and cytokine production by the placental tissue in reaction to the hypoxia, oxidative stress and lipopolysaccharides were measured. The results concluded that hypoxia had no effect on the production of prostaglandins, but interleukin-1beta production increased 15 fold. Oxidative stress increased prostaglandin production 15 fold and increased cytokine (interleukin-1alpha, interleukin1-beta, interleukin-6 and tumour necrosis factor-alpha) production 130 fold.

Another study by Benyo, et al. [28] in 1997 reported similar results. The human placenta apparently produces increased levels of interleukins under hypoxic circumstances. It seems likely that maternal hypoxaemia, resulting from pulmonary disease, such as HIV-related pneumonia, could induce a similar response in the placenta. The dual outcomes of fetal hypoxia and preterm labour would be expected in such circumstances [7].

This study found that almost 60% of the patients experienced some form of preterm delivery, in the apparent absence of infection of the amniotic fluid and membranes.

If it is true that a hypoxic state can induce the normal placenta to produce pathologically increased levels of cytokines, it is possible that maternal hypoxaemia, caused by the pulmonary infection, and not chorioamnionitis, resulted in placental production of interleukins, which then induced preterm contractions.

Furthermore, almost one third of fetuses had evidence of some hypoxic process affecting them, in the form of intrauterine growth restriction, intrauterine fetal death or fetal distress with or without labour.

The same can be said of the fact that the same interleukins as seen in the studies about preterm labour and hypoxic states of the placenta are also the

interleukins which are connected with the mechanism of miscarriages. Therefore it can be deduced that the increased incidence of miscarriage can be due to the same hypoxic process resulting in the increase of the same interleukins, leading to preterm delivery – only at a gestational age where the fetus is not yet viable.

It is impossible to prove that the mechanism suggested is indeed true in the context of this study. This theory can only be validated in further research where samples of amniotic fluid in a similar study group are tested for interleukin content. Simultaneous microscopy and culture of these samples should be done to exclude intrauterine infection. In addition, maternal hypoxia would have to be present in patients with high interleukin levels in the amniotic fluid to prove this suggestion true.

6.8 Reproductive rights of HIV-infected individuals in South Africa

It is clear that pregnancy probably has an adverse effect on the general health of the HIV-infected mother and in some cases also speeds up the progress of the disease. The question therefore remains whether such patients have to be advised against pregnancy, or even be offered termination.

From an ethical point of view and also regarding this country's charter of rights, the autonomy of the patient should be respected, but informed decisions would be the ideal. A planned pregnancy in correlation with the mother's general health and CD4 count, together with counselling about the possible effects of the

pregnancy on the disease, should be the aim. Antiretroviral therapy should play a key role not only in prevention of mother-to-child-transmission, but also preservation of maternal health in the latter stages of AIDS.

In general, the HIV positive mother should not be denied the right to motherhood purely on the basis of her status alone. Cultural aspects are of importance in this setting, where a barren woman can easily be excluded from the community and abandoned by her husband [29].

The adverse effect of pregnancy on the progression of HIV disease is reason for concern. HIV positive women should ideally be counselled to fall pregnant only when in good health and with high CD4 counts. Consideration should be given to the possibility of termination of pregnancy for the sake of maternal health when these parameters are not met.

7. Limitations

The retrospective nature of this study made data collection entirely dependent on what was in the notes. Missing and incorrect data proved to be a problem. CD4 counts, for example, were not always documented despite notes being made of the test being done. Because of the long time period researched (16 years), it was not always possible to locate information if it was not recorded.

Furthermore, follow-up information on the live-born infants was not available past a few days of life. With paediatric care being given in a different department and the babies having different files from mothers, it was also impossible to locate these children.

A number of maternal deaths do occur in the medical and surgical wards of Chris Hani Baragwanath Hospital and these may have been missed. When mothers present with serious medical or surgical problems they are sometimes admitted in the relevant ward and not in the maternity ward. It also happens that mothers are treated elsewhere in the hospital without the pregnancy being noticed initially. In such cases treatment is continued in the original wards of admission and the obstetricians visit daily to monitor the progress of the pregnancy. There is no known mechanism for finding records of such deaths. Patients who died at home could also not be reported here.

The definition of AIDS, despite the clear criteria set out above, might not have been applied in some patients because of the presence of unresolved and untreated pathology. Some patients could not be included in the study, despite having clear evidence in the file of being HIV positive, because no clear note was made that a test was done or that a result was obtained.

8. Conclusion

The overwhelming majority of maternal deaths were related to a respiratory cause in the form of PCP, tuberculosis and community acquired pneumonia. One can assume that pulmonary disease resulting in death will lead to significant hypoxaemia. This is well known to have widespread metabolic consequences in the body, including acidosis and vasoconstriction.

A large number of fetuses in this research project also displayed evidence of possible hypoxia. Fetal distress, as seen on cardiotocograph, intrauterine growth restriction and intrauterine death were observed. These phenomena can all be traced back to fetal hypoxia – further evidence of an oxygen shortage experienced by both mother and child.

A very high proportion of women also had preterm labour. In the preceding discussion, evidence was given that could link preterm labour to raised levels of interleukins in the amniotic fluid. Previous publications entertained the idea that an increase in interleukin levels, in the setting of preterm labour is linked to infection.

As reported, the same interleukins that cause preterm labour are also the ones that could be responsible for the increased rates of spontaneous miscarriage among HIV-infected women.

However, it has been proven that hypoxia and oxidative stress can cause the placenta to start producing the very same interleukins. The conclusion can therefore be made that patients with end stage AIDS, being more prone to pulmonary infections and thus to hypoxia, develop preterm labour indeed as a result of the production of interleukins into the uterine cavity. The difference is that the interleukin production could well be due to the hypoxic state, and not due to an infective process.

The implication for the management of the pregnant HIV patient is evident. Pulmonary infection should be avoided if possible during pregnancy to prevent preterm labour and delivery of a compromised premature infant. It seems, in the light of these findings, that aggressive prevention and treatment of PCP and tuberculosis are crucial. Patients should also have access to antiretroviral treatment to maintain reasonable immune responses. Antiretroviral drugs should possibly be offered at higher CD4 counts than 200 x $10^6/\ell$ and prophylactic administration of cotrimoxazole should be part of the protocol of any antiretroviral regimen.

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***APPENDIX A* – Datasheet used to collect information from AIDS-related maternal death files at Chris Hani Baragwanath Hospital from 1990 to 2005**

Subject no: _____

Age: _____ Parity: _____ Gravida: _____

Rh: _____ RPR: _____ CD4: _____

Date of admission: _____

Summary of disease progression:

_____

_____

_____

_____

_____

GA at delivery/death: _____

Cause of death: _____

Date of death: _____

Obstetric complications:

_____

_____

_____

_____

Booked: _____ Visits: _____

ANC History:

_____

_____

Neonatal outcome: Alive Dead

_____

APPENDIX B – Ethics approval letter from the University of Witwatersrand Human Research Ethics Committee

APPENDIX C – Letter to the University of Witwatersrand Human Research Ethics Committee stating change of title of the research project and surname of researcher

1164 Woodlands Drive
Queenswood
Pretoria
0186
3 April 2007

Sir/Madam

Human Ethics Committee (Medical)
University of the Witwatersrand
Private Bag 3
Wits
2050
South Africa

Particulars regarding the research of Dr Berna Jordaan.

Please note the following about the research that was approved by the Committee last year:

1. The title of the paper was changed in guidance of the MMed Committee of the University of the Witwatersrand, Postgraduate office from
   - In Maternal Deaths Related to AIDS, Is There a Trend Towards Certain Obstetric Complications?

   TO
   - Obstetric Complications in Maternal Deaths Related to AIDS.

   The fundamentals of the research remain exactly the same, only the title was changed.

2. My surname has changed as well as my address, as I got married on the 23rd of December 2006. Jordaan was my previous married name and I am therefore changing it to my new married name. My registration at the HPCSA has also been changed accordingly. I include a copy of my marriage certificate. My new surname is Venter.

Thank you.

Dr B Venter (082 3388 976)