



HIV-associated maternal mortality – primary causes of death at King Edward VIII Hospital, Durban

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Background. The maternal mortality ratio in poor countries is reported to be 650/100 000 live births. This high maternal mortality may be associated with increasing numbers of HIV-related deaths in sub-Saharan Africa.

Objective. To establish the direct causes of maternal mortality related to the HIV syndrome.

Methods. A retrospective analysis was done of 378 maternal deaths at King Edward VIII Hospital, Durban, between January 1998 and December 2004.

Results. The commonest cause of death related to HIV was World Health Organization (WHO) clinical classification stage IV disease, followed by pneumonia (bacterial and *Pneumocystis carinii* pneumonia), pregnancy-related sepsis and pulmonary tuberculosis.

Conclusion. HIV/AIDS has a great impact on maternal mortality in South Africa, mainly because of the increasing incidence of this syndrome in women in their early reproductive years.

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HIV/AIDS is an extraordinary global epidemic. The epidemic is extremely dynamic, growing and changing in character.¹ In 2003, 5 million people became infected with HIV worldwide, with almost 3 million of these newly infected cases living in sub-Saharan Africa. At a global level, the number of infected people continues to rise, from 35 million in 2001 to 38 million in 2003, and almost 3 million died from AIDS in the same year.¹ An estimated 25 million people are living with HIV in sub-Saharan Africa. Furthermore, women are at greater risk, becoming infected at an earlier age than men. On average there are 13 infected women for every 10 infected men in sub-Saharan Africa.¹

The reporting of enquiries into maternal deaths is relatively new in South Africa, the first report having been published in 1999.² The maternal mortality ratio (MMR) in a country such as the UK is 10/100 000 maternities, while in poor countries it is as high as 650/100 000 live births.³ In South Africa, a middle-income country, the National Committee on Confidential Enquiries into Maternal Deaths reported a MMR of 150/100 000 live births for 1998, while the latest Saving Mothers Report indicates a MMR of 175 - 200/100 000 live births for 1999 - 2001.^{2,3} In 1992 the 5 major causes of maternal death in South Africa were in ranked order: hypertensive disorders of pregnancy, pregnancy-related sepsis, obstetric haemorrhage, non-pregnancy-related sepsis (mainly HIV/AIDS), and pre-existing medical conditions.²

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The commonest cause of death in the triennial report for 1999 - 2001³ was non-pregnancy-related infections (HIV/AIDS). The fact that deaths from non-pregnancy-related infections is high is indicative of the impact of HIV in South Africa and is probably in keeping with the increasing HIV prevalence rate among pregnant women attending public health care facilities.

HIV prevalence has been increasing since 1990 in South Africa.⁴ Data from antenatal surveillance studies show rates from 0.7% in 1990 to 28% in 2001.⁴ The prevalence of HIV in KwaZulu-Natal (KZN) is the highest in South Africa (37.5%).⁴ Although pregnancy-related sepsis associated with HIV/AIDS is the commonest cause of maternal mortality, direct causes of HIV-related maternal deaths have not been established.

Objective

The aim of the study was to establish the causes of maternal death associated with HIV in the last 7 years at King Edward VIII Hospital (KEH), Durban, South Africa.

Methods

Records of all maternal deaths that occurred at KEH and summaries of the detailed audit of the deaths were analysed. The study period included the years between January 1998 and December 2004. It should be noted that KEH is the major tertiary referral centre for KZN, a province with a population of 9 million.

Maternal death was defined as the death of a woman while pregnant or within 42 days of termination of pregnancy, from any cause related to or aggravated by the pregnancy or its management, but not from accidental or incidental causes. The notification process requires that all maternal deaths occurring during pregnancy or within 42 days of being pregnant be reported to the National Department of Health (DOH) in South Africa. These deaths are then classified as direct, indirect



and fortuitous deaths. The MMR is defined as the number of maternal deaths per 100 000 live births. Audits of all maternal deaths are carried out by trained assessors and the causes of death are assigned as primary and contributory causes.

The World Health Organization (WHO) clinical staging of HIV was used to classify the severity of the syndrome.³ The staging is as follows: stage I – asymptomatic; stage II – unintentional weight loss < 10% body weight and evidence of herpes zoster in the last 5 years; stage III – bedridden < 50% of the time and unintentional weight loss of > 10% body weight; and stage IV – bedridden > 50% of the time, HIV wasting, *Pneumocystis carinii* pneumonia (PCP), central nervous system toxoplasmosis, cryptococcal meningitis, Kaposi's sarcoma, HIV encephalopathy and oesophageal candidiasis. The diagnosis of HIV was only made if an HIV test was positive. Women who did not have an HIV test but who had clinical signs of the disease were not included in the analysis. Descriptive statistics were used and all results are presented as frequency, means, medians and percentages.

Results

There were 51 527 births and 378 deaths in the 7-year period between January 1998 and December 2004. The MMR was therefore 733/100 000 live births.

The demographic data are shown in Table I. The mean age of the HIV-infected women was 27 (17 - 42) years, the median parity was 2 (0 - 6), and the median gestational age 30 (8 - 42) weeks. Of those who had antenatal care and HIV testing, 42.3%

were HIV-infected while 15.2% were negative. The HIV status was unknown in the rest. The median number of days at which death occurred following delivery was 6 (Table I).

The increasing MMR over the 7-year study period is shown in Table II. The MMR was 434/100 000 live births in 1998 and 1 023/100 000 live births in 2004.

Over the 7-year period 38.6% of the deaths occurred in HIV-infected women, and HIV status was unknown in 48.1%. HIV status remained static from 1998 to 2002 and showed a significant increase in 2003 - 2004.

Table III shows the causes of death. WHO stage IV disease was the most common cause of death.

Pregnancy-related sepsis occurred more frequently in HIV-infected than non-infected women, and deaths from pneumonia and pulmonary tuberculosis (TB) occurred only in those who were HIV-positive (Table IV).

Most deaths (62.3%) occurred in the 21 - 30-year age group, while 74.2% presented with stage IV HIV disease.

Of the 24 HIV-infected patients with pregnancy-related sepsis, 11 (45.8%) delivered vaginally and 13 (55.2%) by caesarean section. In contrast, of the 16 HIV-non-infected patients with pregnancy-related sepsis, 7 (43.8%) delivered vaginally and 9 (56.2%) by caesarean section; of the 38 patients whose HIV status was unknown, 21 (55.3%) delivered vaginally and 17 (44.7%) by caesarean section.

Of the remaining 12 patients (of the 90 with pregnancy-related sepsis), 4 were undelivered and 8 did not have the appropriate information.

Table I. Demographic data (N = 378)

Parameter	HIV-negative (N = 50, 13.2%)	HIV-positive (N = 146, 38.6%)	HIV-unknown (N = 182, 48.1%)
Age (years) (mean)	26 (16 - 46)	27 (17 - 42)	27 (13 - 46)
Parity (median)	1 (0 - 11)	2 (0 - 6)	1 (0 - 9)
Gestational age (weeks) (median)	35 (20 - 41)	30 (8 - 42)	32 (8 - 41)
Booked for ANC (N (%))*	36 (15.2)	100 (42.3)	100 (42.3)
Days post delivery (median)	6 (0 - 43)	6 (0 - 37)	6 (0 - 39)

*Booked for antenatal care attendance (at least 2 visits).

Table II. Trends in the MMR and HIV status, 1998 - 2004 (N (%))

Year	Overall MMR	MMR (HIV-associated)	HIV-negative	HIV-positive	HIV-unknown
1998	434	164	7 (18.9)	14 (37.8)	16 (43.2)
1999	520	169	7 (15.9)	14 (31.8)	23 (52.3)
2000	718	225	11 (21.6)	16 (31.4)	23 (52.3)
2001	603	188	2 (4.2)	15 (31.1)	31 (61.6)
2002	1 013	323	9 (12.5)	23 (31.9)	41 (55.6)
2003	983	553	7 (10.9)	36 (56.3)	21 (32.8)
2004	1 023	462	7 (11.3)	28 (45.2)	27 (43.5)

MMR = maternal mortality ratio/100 000 live births.



Discussion

The high MMR and the increasing number of deaths resulting from non-pregnancy-related sepsis are striking findings of this study. The high MMR is probably due to the fact that KEH is a tertiary institution and most high-risk patients and those requiring emergency care in KZN are referred to this health facility. Furthermore, the MMR was calculated for all deliveries at KEH only, and therefore did not include deliveries at the referral sites. Nonetheless, the MMR is high and probably reflects the fact that KZN is largely rural, relatively underdeveloped with poor transport systems and is the epicentre of the AIDS pandemic in South Africa.

The increasing number of deaths over the study period, particularly in the last 2 years, can probably be attributed to better reporting of maternal deaths or to an increasing number of deaths caused by non-pregnancy-related sepsis, mainly HIV/AIDS-related deaths. Non-pregnancy-related sepsis is a term used in the Saving Mothers Report and includes deaths related to infections arising from organ systems other than the reproductive tract, such as pneumonia and meningitis.

Our finding of an increasing number of HIV/AIDS-related deaths is similar to that reported from Harare⁵ where there had been a steady increase in the MMR from 50/100 000 live births in 1988 to 224/100 000 live births in 1997 following a decline in maternal mortality in the late 1970s and early 80s. These authors suggest that the increase in the MMR

is probably because of the impact of HIV/AIDS. It is quite possible that the impact of HIV/AIDS is much greater in our setting because voluntary counselling and testing as a public health programme for the prevention of the mother-to-child transmission only started in South Africa in 2001. Furthermore, uptake of voluntary testing is still in the region of 70% at KEH (2004 KZN Prevention of Mother to Child Transmission Programme – unpublished data); in addition, the criteria for the diagnosis of HIV/AIDS were stringent, and the diagnosis was made only if the HIV serological test was positive and not purely on clinical evidence.

The HIV rates in 2003 and 2004 were very high, probably because of an improvement in the uptake of voluntary testing in KZN. Such improvements in the mother-to-child prevention programme and the recent introduction of the antiretroviral (ARV) rollout programme should result in more accurate data on primary causes of death related to HIV. The commonest cause of death ($N = 31$, 21.2%) associated with HIV/AIDS was stage IV WHO AIDS classification. Furthermore the majority of infected women were in their early (47.4%) and late twenties (48.9%), followed by those in their early thirties (37.7%). This is an obvious cause for concern as young women are dying of stage IV disease, which indicates that they were probably infected in their early teenage years. The survival period in patients with AIDS tends to be short in Africa⁶ because of lack of ARVs and rapid progression of the disease. The median survival is reported to be 9 years (8 - 11 years).⁷ The ARV rollout programme and public health education programme on prevention of HIV/AIDS may result in a positive change in the pattern of deaths.

There are conflicting reports concerning the course of HIV in pregnancy. Kumar *et al.*⁸ reported that pregnancy associated with HIV has a detrimental effect on both maternal and obstetric outcome and accelerates disease progression. They found that as pregnancy progressed, CD4 counts declined in association with HIV-related clinical deterioration. On the other hand Dabis and Ekpini⁷ reported that pregnancy does not affect the course of HIV-1 infection and that this kind of study has not been done in Africa. Furthermore, Weisser *et al.*⁶ indicated that after taking the CD4 count before conception into account, acceleration of disease progression was inconsistent among HIV-infected women.

Table III. Causes of HIV-related maternal mortality (N = 146)

Cause	%	Number
WHO stage IV disease	21.2	31
Pneumonia	19.9	29
Pregnancy-related sepsis*	18.5	27
Pulmonary tuberculosis	15.1	22
Herbal ingestion	1.4	2
Hypertension	4.1	6
Obstetric haemorrhage	4.1	6
Pre-existing medical conditions	5.5	8
Other [†]	8.2	12
Missing information	2.1	3

*Pregnancy-related sepsis (included puerperal sepsis and septic incomplete abortion)
[†]Other – deaths from meningitis, molar pregnancy, adult respiratory distress syndrome, hepatitis and malaria.

Table IV. Cause of death comparing HIV-positive and HIV-negative mothers (N (%))

Cause of death	HIV-positive (N = 146, 38.6%)	HIV-negative (N = 50, 13.2%)	HIV-unknown (N = 182, 48.1%)	p-value
Pregnancy-related sepsis	27 (30)	16 (17.8)	47 (52.2)	0.104
Pneumonia	29 (90.6)	0 (0)	3 (9.4)	< 0.001
Pulmonary tuberculosis	22 (88)	0 (0)	3 (12)	< 0.001
Hypertension	6 (8.6)	11 (15.7)	53 (75.7)	< 0.001



The second commonest cause of death associated with HIV/AIDS was pneumonia ($N = 29$, 19.9%) mainly a combination of bacterial pneumonia and PCP. Most of the published data on pulmonary complications are from studies involving non-pregnant patients. The effects of pregnancy on respiratory diseases associated with HIV infection and vice versa are not well documented. Lim *et al.*⁹ reported that the incidence and mortality of pneumonia in pregnancy is similar to that in the non-pregnant state, but these authors did not report on the HIV status of their patients. HIV-infected patients are reported to be at risk of recurrent bacterial pneumonia which carries a worse prognosis.⁹

Kruger and Bhagwanjee¹⁰ also reported that the leading cause of maternal death at Johannesburg Hospital in 2000/2001 was pneumonia. In addition, pneumonia was found to be the second commonest cause of maternal HIV-related death in South Africa.³ The course of pneumonia in pregnancy has been found to be more virulent, with high mortality.¹¹ A number of physiological and hormonal changes occur in the pregnant host that specifically predispose to pneumonia, with the major factor being an alteration in immune status.¹¹

PCP is a common cause of respiratory failure and ICU admissions, and accounts for 50% of HIV-associated mortalities among pregnant women in the USA.¹² Prophylactic cotrimoxazole is therefore recommended for use in all patients with a CD4 count $< 200/\mu\text{l}$, but caution should be exercised in pregnant women during the first trimester because of the known teratogenic effects of this drug.

Pregnancy-related sepsis accounted for 18.5% of the HIV deaths. This included puerperal sepsis related to viable pregnancies and septic incomplete abortion. Caesarean sections were performed in 48.1% compared with 40.7% of vaginal births. It is well known that postpartum sepsis is 3.2 times more likely to occur after caesarean section than after vaginal delivery and HIV infection impacts negatively on this rate.¹³ A study by Ferrero and Bentivoglio¹⁴ showed that 64.5% of HIV-infected women had a complicated recovery after surgery. HIV-positive women with CD4 counts less than $500/\mu\text{l}$ had higher post-caesarean section morbidity than HIV-infected women with CD4 counts over 500. Zishiri *et al.*¹⁵ therefore recommend a review within the first 2 weeks post delivery in addition to the routine 6-week check. The Saving Mothers 2001 report³ recommends that women should be reviewed within 7 days of discharge.

Pulmonary tuberculosis was the fourth commonest cause of HIV-related maternal death (15.1%, $N = 22$). The lifetime risk of an HIV-negative person contracting TB is 10% compared with 10% for each year of life in someone who is HIV-infected. It has been emphasised that TB and AIDS epidemics are linked as TB is the most common opportunistic infection in people with AIDS.³ However, because of the high TB prevalence in South Africa (60%), TB may occur at varying degrees of immunosuppression.

A review of the literature¹⁶ found that of all maternal TB deaths, 54% were attributable to HIV infection. Recent statistics indicate that the incidence of TB in pregnancy is increasing. Higher birth rates in women at risk, coupled with the AIDS epidemic are the chief underlying factors.¹⁷ Opinions about the influence of pregnancy on the prognosis for TB have varied widely. Good data are now available to suggest that there is no increased risk of progression for women in pregnancy or postpartum compared with non-pregnant women of the same age.¹⁷ Restoration of immune function with the use of highly active antiretroviral therapy (HAART) will have a positive impact on HIV-related maternal mortality. An analysis by Badri *et al.*¹⁷ suggests that starting patients on HAART will result in prevention of 14 - 20 cases of TB per 100 patient-years of treatment.

In conclusion, the HIV epidemic is resulting in a changing pattern of major causes of maternal mortality in South Africa. In the absence of the use of ARV therapy, maternal mortality due to the HIV epidemic in the study period was mainly associated with WHO stage IV disease, followed by pneumonia, pregnancy-related sepsis, and pulmonary TB. The National DOH's comprehensive care and management plan for HIV that has recently been implemented, may result in a reduction of maternal mortality and/or a changing pattern of the main causes of death.

References

1. UNAIDS. *Executive Summary: 2004 Report on the Global AIDS Epidemic*. Geneva: UNAIDS, 2004.
2. Department of Health. *Saving Mothers: Report on Confidential Enquiries into Maternal Deaths in South Africa 1998*. Pretoria: DOH, 1999.
3. Department of Health. *Saving Mothers: Second Report on Confidential Enquiries into Maternal Deaths in South Africa, 1999 - 2001*. Pretoria: DOH, 2002.
4. Department of Health. *2001, 2002 and 2003 National HIV and Syphilis Seroprevalence Survey of Women Attending Public Antenatal Clinics in South Africa*. Summary Report, Pretoria: DOH, 2004.
5. Majoko F, Chipato T, Iliff V. Trends in maternal mortality for the greater Harare Maternity unit: 1976-1997. *Cent Afr J Med* 2001; 47: 199-203.
6. Weisser M, Rudin C, Bategay M, *et al.* Does pregnancy influence the course of HIV infection? Evidence from two large Swiss cohort studies. *J Acquir Immune Defic Syndr Hum Retroviro* 1998; 17: 404-410.
7. Dabis F, Ekpini ER. HIV-1/AIDS and maternal and child health in Africa. *Lancet* 2002; 359: 2097-2104.
8. Kumar RM, Uduman SA, Khurana AK. Impact of pregnancy on maternal AIDS. *J Reprod Med* 1997; 42: 429-434.
9. Lim WS, MacFarlane JT, Colthorpe CL. Treatment of community-acquired lower respiratory tract infections during pregnancy. *Am J Respir Med* 2003; 2: 221-233.
10. Kruger AM, Bhagwanjee S. HIV/AIDS Impact on maternal mortality at the Johannesburg Hospital, South Africa: 1995 - 2001. *Int J Obstet Anesth* 2003; 12: 164-168.
11. Goodrum LA. Pneumonia in pregnancy. *Semin Perinatol* 1997; 21: 276-283.
12. Ahmad H, Melta NJ, Manikal VM. *Pneumocystis carinii* pneumonia in pregnancy. *Chest* 2001; 120: 666-671.
13. Kankuri E, Kurki T, Carlson P, *et al.* Incidence, treatment and outcome of peripartum sepsis. *Acta Obstet Gynecol Scand* 2003; 82: 730.
14. Ferrero S, Bentivoglio G. Post-operative complications after caesarean section in HIV infected women. *Arch Gynecol Obstet* 2003; 268: 268-273.
15. Zishiri C, Shodu LK, Tshimanga M, *et al.* Postnatal maternal morbidity patterns in mothers delivering in Gweru city (Midlands Province). *Cent Afr J Med* 1999; 45: 234-239.
16. Khan M, Pillay J, Moodley J. Maternal mortality associated with tuberculosis-HIV co-infection in Durban, South Africa. *AIDS* 2001; 15: 1857-1863.
17. Badri M, Wilson D, Wood R. Effect of highly active antiretroviral therapy on incidence of tuberculosis in South Africa: a cohort study. *Lancet* 2002; 359: 2059-2064.

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