Mothers infected with HIV

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The HIV/AIDS epidemic intersects with the problem of maternal mortality in many circumstances. The extent of the contribution of HIV/AIDS to maternal mortality is difficult to quantify, as the HIV status of pregnant women is not always known. HIV infection and AIDS-related deaths have become one of the major causes of maternal mortality in many resource-poor settings. HIV impacts on direct (obstetrical) causes of maternal mortality by an associated increase in pregnancy complications such as anaemia, post-partum haemorrhage and puerperal sepsis. HIV is also a major indirect cause of maternal mortality by an increased susceptibility to opportunistic infections such as Pneumocystis carinii pneumonia, tuberculosis and malaria. Appropriate antiretroviral therapy started in pregnancy could reverse the toll of HIV-related maternal mortality. Without such efforts and increased HIV prevention, the gains achieved by safe motherhood programmes will be lost in the future.

Two intersecting epidemics

The HIV/AIDS epidemic intersects with the problem of maternal mortality in many circumstances. Almost half of the 42 million people living with HIV are women in their reproductive years. Across the world, over 2 million HIV-infected women are pregnant each year, over 90% of them in developing countries, while close to 600,000 women die each year from complications of pregnancy and childbirth, the majority of them also in resource-constrained settings. The extent of the contribution of HIV/AIDS to maternal mortality is difficult to quantify, as the HIV status of pregnant women is not always known. Although programmes to prevent mother-to-child transmission of HIV have expanded dramatically in many countries over the past few years, most pregnant women in high prevalence areas still do not have access to HIV counselling and testing.

HIV infection rates in pregnant women range from below 1% to over 40% in different countries. The highest rates are still in Africa, although prevalence in some Asian countries has risen considerably. Prevalence rates have fallen in some areas, such as Uganda, and there are encouraging signs that rates in young women are beginning to fall in South Africa and some other sub-Saharan settings, but the prevalence remains high in...
many others. As the epidemic becomes more established in many countries, increasing numbers of pregnant women are being encountered who have been infected for longer and present with HIV/AIDS complications, which will impact on maternal mortality rates. By the mid 1990s in Tanzania, AIDS was the leading cause of death for women in the reproductive age group, a situation now common to many resource-poor countries. There is some evidence for a decrease in fertility in high HIV prevalence settings, which may reduce the risk of maternal mortality from AIDS-related causes, although HIV/AIDS remains the leading cause of death in adults in these areas.

HIV/AIDS may influence maternal mortality in several ways. Women living with HIV/AIDS may be more susceptible to direct or obstetric causes of maternal mortality, such as post-partum haemorrhage, puerperal sepsis and complications of caesarean section. AIDS-related deaths may be incidental to the pregnancy (fortuitous) or may be true indirect causes of maternal mortality where the infection itself or opportunistic infections such as tuberculosis progress faster in the pregnancy. There is growing evidence for the impact of the AIDS epidemic on maternal mortality rates and for the effect of AIDS-related complications on maternal deaths.

The effect of AIDS on maternal mortality: changing the causes of maternal mortality

The maternal mortality ratio (MMR) in resource-poor settings is 10–100 times that of industrialized countries. Rates in these countries can be over 1000 per 100,000 live births compared to less than 10 in resource-rich settings. In South Africa, where maternal mortality rates are lower than in most African countries, the MMR from the country’s first national report on maternal deaths in 1998 was 12.3 times higher than that of the UK, partly attributable to HIV/AIDS. In addition, severe maternal morbidity may be up to 10 times more common than mortality.

In the past, direct obstetric causes have been responsible for most of the deaths of mothers, with the majority attributed to haemorrhage, hypertension, obstructed labour and abortion complications. This pattern is changing in many places as AIDS-related complications now account for a high proportion of maternal deaths. The trio of AIDS, tuberculosis and malaria have become more important as causes of maternal mortality.

AIDS has also become a contributing cause of maternal mortality in developed countries, although much smaller in numbers, despite better access to appropriate care. Before the widespread availability of highly active antiretroviral therapy (HAART), the risk of maternal death from HIV/AIDS was highest in the first trimester of pregnancy, when women were least likely to seek antenatal care and were generally unaware of their HIV status. However, with the introduction of HAART, the risk of maternal death from AIDS-related causes has been reduced, and antenatal care has become more accessible, leading to improved outcomes for both mother and child.
active antiretroviral therapy (HAART), AIDS was becoming a leading cause of maternal mortality in some areas of the USA. A retrospective study in New Jersey, USA, showed a rise in maternal mortality in the early 1980s, with a decrease in deaths from direct obstetric causes and AIDS the major cause of pregnancy-related mortality. In areas of Europe with high levels of immigrant populations, a similar pattern is seen. With better access to HAART, mortality has decreased in people with AIDS, and current treatment recommendations support the use of appropriate antiretroviral treatment in pregnant women, which will reduce the rates of AIDS complications seen during pregnancy. In most resource-poor settings, however, this level of treatment is unavailable to date, and HIV/AIDS remains a major problem.

Several African and Asian studies in the 1990s demonstrated the increasing role of AIDS and related illnesses as causes of maternal mortality. MMRs in these studies ranged from 400 to over 900 per 100,000 live births. A study in Zambia showed that rates of maternal mortality increased eight-fold over the past two decades, despite better obstetric services. Indirect causes of maternal mortality were responsible for 58% of deaths, with malaria and AIDS-related tuberculosis the most common of these. In the Rakai district of Uganda, maternal mortality was five times higher in HIV-positive women than in HIV-negative women, reaching rates of over 1600 per 100,000 live births in the infected group. In Malawi and Zimbabwe, pregnancy-related mortality has increased 1.9 and 2.5 times, in parallel with the increasing AIDS epidemic.

AIDS-related deaths were the primary cause of death in mothers in Brazzaville in 1993, while AIDS was the fourth highest cause of maternal mortality in a Tanzanian district. In India, a study in AIDS symptomatic women showed high rates of maternal mortality. Pneumocystis carinii pneumonia (PCP) followed by miliary tuberculosis and wasting disease were the most common AIDS-defining illnesses and causes of maternal death.

In South Africa, a national confidential enquiry into maternal deaths was instituted in 1998. AIDS was the second most common cause of maternal death in 1998, accounting for 13% of all deaths in the first year. In the years 1999–2001, AIDS was the listed cause of death in 17% of cases, although this figure may be considerably underestimated as HIV status was known in only 36% of cases.

Maternal dietary deficiencies may exacerbate the progression of HIV. Vitamin A deficiency has been shown to be associated with more rapid disease progression in HIV-infected women, increased rates of transmission of HIV from mother to child and higher levels of viral load in breast milk. Vitamin A supplementation has not been shown to reduce the risk of mother-to-child transmission, but there is little information on the
effect on maternal health in HIV-infected women. A large study in a general population in Nepal showed that supplementation with vitamin A or beta carotene reduced maternal mortality by 44%\textsuperscript{21}. In Tanzania, multivitamin supplementation, but not vitamin A alone, resulted in significant increases in CD4, CD3 and CD8 counts\textsuperscript{22}. Further research may be indicated to investigate the role of vitamin supplementation in reducing maternal mortality and morbidity on HIV-positive women\textsuperscript{23}.

The effect of pregnancy on HIV/AIDS progression

Data available from developed countries suggest that pregnancy does not accelerate the progression of HIV disease\textsuperscript{24–27}. A systematic review and meta-analysis of seven cohort studies from 1983 to 1996 suggested that there was an association between adverse maternal outcomes and pregnancy in HIV-infected women. The summary odds ratios for the risk of an adverse maternal outcome related to HIV infection and pregnancy were 1.8 (85\% CI 0.99–3.3) for death, 1.41 (95\% CI 0.85–2.33) for HIV disease progression and 1.63 (95\% CI 1.00–2.67) for progression to an AIDS-defining illness. This association appeared to be stronger in the one study in this group conducted in a resource-poor setting.

The effect of HIV on mothers is not limited to the period included in maternal mortality figures, and figures correlating HIV infection and maternal mortality may underestimate the combined effects of the two conditions. While little effect on disease progression is described in the post-pregnancy period in resource-rich settings\textsuperscript{28}, or in Thailand\textsuperscript{29}, there is evidence from several studies in Africa that the mortality of HIV-infected women is also high in the post-pregnancy period.

In a prospective study of anti-malaria prophylaxis in over 4000 mothers in Malawi, the maternal mortality rate was 370 per 100,000 women and the mortality rate between 6 weeks and 1 year post-partum was 341 per 100,000 live births. AIDS and anaemia were the major causes of post-pregnancy mortality\textsuperscript{30}. In Zaire, maternal mortality rates in HIV-infected women were 10 times those of HIV-negative women\textsuperscript{31}, with 22\% of HIV-infected mothers dying during a 3-year follow-up period.

John and colleagues have shown an interesting correlation between CCR5 promoter polymorphisms and increased mortality post-pregnancy in a Kenyan cohort\textsuperscript{32}. In this report, women with the 59356 C/T genotype had a 3.1-fold increased risk of death during the 2-year follow-up period (95\% CI 1.0–9.5) and a significant increase in vaginal shedding of HIV-1-infected cells (odds ratio 2.1; 95\% CI 1.0–4.3), compared with women with the 59356 C/C genotype. This suggests that there may be multiple factors, including nutritional and genetic, that influence the risk of faster progression during and post pregnancy.
Effect of HIV/AIDS on pregnancy complications

Obstetric causes of maternal morbidity and mortality may be more severe in women infected with HIV, and they may be more susceptible to infectious and post-surgical complications\(^{25,33}\). These include higher reported rates of ectopic pregnancy, early abortion, bacterial pneumonia, urinary tract infection, oral and recurrent vaginal thrush and other infections. Malaria and tuberculosis have become major complicating conditions in HIV-infected pregnant women. Anaemia may be much more frequent and severe in HIV-infected women, and especially so where pregnancy is complicated by malaria.

Post-partum and post-caesarean section complications have been described in some studies. Post-partum haemorrhage has been described as more common in some studies\(^{17}\), and may be more serious if associated with pre-existing anaemia in HIV-infected women. Post-partum morbidity occurred in 15% of 1186 deliveries during 1990–1998 in The Women and Infants Transmission Study in the United States\(^{34}\). The most commonly reported post-partum morbidity events were: fever without infection, haemorrhage or severe anaemia, endometritis, urinary tract infection and caesarean wound complications. Post-caesarean section complications have been higher in some studies, particularly in those women who are severely immunosuppressed, but this is less likely where antibiotic prophylaxis is provided\(^{35,36}\).

It has been suggested that the rate of pre-eclampsia is lower in HIV-infected women who do not receive antiretroviral treatment than in treated women or HIV-negative controls\(^{37}\). This association has not been confirmed to date in other cohorts. An underestimated cause of significant morbidity and some mortality in HIV-infected women is mental illness. A study in Zambia of women diagnosed as HIV-infected during pregnancy showed that the majority of women (85%) showed major depressive episodes and had significant suicidal thoughts\(^{38}\).

HIV-related opportunistic infections

Several opportunistic infections associated with HIV infection may complicate pregnancy and cause maternal mortality. PCP has a more aggressive course during pregnancy, with an increase in both morbidity and mortality. Several case reports have illustrated the impact of PCP and the difficulties of treatment in pregnancy\(^{39–42}\). Other pulmonary diseases have been described more rarely in pregnancy, and these include bacterial infections (\textit{Haemophilus influenzae} and \textit{Streptococcus pneumoniae} along with \textit{Pseudomonas aeruginosa}), fungal infections
(Cryptococcus neoformans, Histoplasma capsulatum and Coccidioides immitis), viral infections (cytomegalovirus) and opportunistic neoplasms (Kaposi’s sarcoma, lymphoma)\(^4^3\). The extent to which pregnancy affects the course of these respiratory diseases in HIV-infected women is not well described. In general, management is similar to the non-pregnant state, but delays in diagnosis and treatment may influence the course of disease.

Less common but potentially fatal opportunistic infections described in pregnant women include disseminated herpes zoster\(^4^4\) and cerebral toxoplasmosis\(^4^5\).

**Tuberculosis**

One of the major contributing factors to maternal mortality in HIV-infected women is concurrent tuberculosis (TB) infection. TB is one of the leading infectious causes of death in women in the reproductive age group worldwide\(^4^6,4^7\). It is also the most common opportunistic infection associated with HIV in resource-poor settings, and the two epidemics of HIV and TB have had a synergic effect on each other.

An association between an increase in maternal mortality from TB was reported from Zambia in 1999\(^1^4\). A further study in Durban, South Africa, investigated 101 maternal deaths out of 50,518 deliveries\(^4^8\). In this group the MMR was 323 per 100,000 live births for HIV-infected mothers and 148 per 100,000 live births for HIV-negative mothers. The mortality rate for HIV and TB co-infection was 121/1000, three times that of TB without concurrent HIV infection. The authors concluded that 54\% of maternal deaths due to TB were attributable to HIV infection.

It is likely that this increased susceptibility to TB complications will continue to be a major cause of maternal mortality in high prevalence HIV areas\(^4^9,5^0\).

**Malaria**

Over the past 5 years, there has been increasing evidence of an association between malaria in pregnancy and HIV infection\(^5^1-5^4\). HIV increases the risk of malaria in women of all gravidities, although the mechanism of this association is unclear. The standard recommended intermittent therapy regimens of sulfadoxine–pyrimethamine may be insufficient to clear parasitaemia in these women and may need to be reassessed\(^5^5\).

Given the role of malaria as a potential cause of maternal mortality, the association of a higher prevalence of disease in HIV-infected women, the anaemia associated with both diseases and the potential interaction, more research is needed to determine appropriate control strategies.
Antiretroviral treatment

The major determinant of a fall in AIDS-related mortality in resource-rich settings has been the availability of antiretroviral treatment. In most resource-poor settings, antiretroviral treatment has not yet become widely available.

Guidelines from the United States Public Health Service, the World Health Organization and others recommend the appropriate use of antiretroviral treatment for pregnant women, as indicated by their clinical and immunological status\(^1\,\(^{11}\,\(^{56}\)).

If the impact of HIV on maternal mortality is to be controlled and reversed, appropriate use of antiretroviral treatment is essential\(^{13}\). While many countries have initiated programmes to reduce mother-to-child transmission of HIV, these will have to be expanded to include care of mothers. With increasing access to these drugs, health workers will have to be trained to identify women in need of treatment and to initiate and monitor treatment during pregnancy. Without such interventions, the efforts of safer motherhood and safe pregnancy programmes over the past two decades will be reversed as maternal mortality due to HIV/AIDS continues to rise.

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