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HIV and maternal mortality☆

Eva Lathrop[a,*], **Denise J. Jamieson**[b], and **Isabella Danel**[b]

[a] Centers for Disease Control and Prevention, Atlanta, GA, USA

[b] Division of Reproductive Health, National Center for Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, GA, USA

Abstract

The majority of the 17 million women globally that are estimated to be infected with HIV live in Sub-Saharan Africa. Worldwide, HIV-related causes contributed to 19 000–56 000 maternal deaths in 2011 (6%–20% of maternal deaths). HIV-infected pregnant women have two to 10 times the risk of dying during pregnancy and the postpartum period compared with uninfected pregnant women. Many of these deaths can be prevented with the implementation of high-quality obstetric care, prevention and treatment of common co-infections, and treatment of HIV with ART. The paper summarizes what is known about HIV disease progression in pregnancy, specific causes of HIV-related maternal deaths, and the potential impact of treatment with antiretroviral therapy on maternal mortality. Recommendations are proposed for improving maternal health and decreasing maternal mortality among HIV-infected women based on existing evidence.

Keywords

HIV; Maternal mortality; Pregnancy; Sub-Saharan Africa

1. Introduction

An estimated 17 million women globally are living with HIV. The majority of these women live in Sub-Saharan Africa and are of reproductive age (15–49 years) [1]. Estimates of maternal death due to HIV-related causes vary widely. In 2011, HIV-related causes contributed to between 19 000 [2] and 56 000 maternal deaths [3], accounting for between 6% and 20% of maternal deaths globally and likely a much higher proportion of deaths in Sub-Saharan Africa [2,3]. Globally over the past two decades, maternal mortality has decreased. However, reductions in Sub-Saharan Africa have not kept pace with other parts of the world, making it unlikely that many countries in this region will achieve Millennium Development Goal 5 (MDG 5). The HIV pandemic has contributed to this lack of progress.

☆The findings and conclusions in the paper are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

* Corresponding author at: Centers for Disease Control and Prevention, 1600 Clifton Rd, Atlanta, GA 30333, USA. Tel.: +1 770 833 1884; fax: +1 770 404 778. elathro@emory.edu (E. Lathrop)..

Conflict of interest

The authors have no conflicts of interest.

HIV-infected pregnant women have two to 10 times the risk of dying during pregnancy and the postpartum period compared with uninfected pregnant women [4–8].

The present paper summarizes what is known about HIV disease progression in pregnancy, the specific causes of HIV-related maternal deaths, and the potential impact of treatment with antiretroviral therapy (ART) on maternal mortality. We propose recommendations for improving maternal health and decreasing maternal mortality among HIV-infected women based on existing evidence.

2. HIV disease progression in pregnancy

Pregnancy does not appear to accelerate the progression of HIV disease. Although some of the studies addressing this issue come from high-income countries where women had various treatment options [9], studies from low-income countries in which there was no treatment available report similar findings [9]. While studies generally agree that there is no HIV disease progression during pregnancy, there is a suggestion that pregnancy (or perhaps breastfeeding) may accelerate disease progression after delivery [10]. There is no evidence of an increased risk of deaths due to HIV among HIV-infected pregnant women compared with HIV-infected nonpregnant women [11]. In fact, HIV-infected women who are not pregnant have significantly higher mortality rates than their pregnant counterparts [4,12]. Advanced HIV disease is associated with lower fertility rates. HIV-infected pregnant women are generally healthier than nonpregnant HIV-infected women and they are less likely to be in the later stages of disease and as a group have less HIV-attributable mortality than nonpregnant HIV-infected women [5].

3. Causes of maternal death among HIV-infected women

WHO defines maternal deaths as those that occur during pregnancy or within 42 days of termination of pregnancy from either direct or indirect causes [13]. Deaths in HIV-infected pregnant women arise from both direct causes (those directly caused by the pregnancy or its management) and indirect causes (those in which the pregnancy contributed to a death from another condition), which are largely infectious in low-income settings. The direct and indirect causes are each responsible for a variable proportion of maternal deaths, depending upon the region, setting, and prevalence of other infectious diseases. The proportion of deaths attributed to indirect causes has been reported to be greater than 50% in some settings, and some of the highest contributors to indirect deaths in the HIV-infected pregnant population include AIDS, tuberculosis, malaria, and pneumonia, among others [8]. The direct causes that contribute to a greater risk of death in the HIV-infected compared with the uninfected pregnant woman include puerperal sepsis and sepsis related to abortion [8].

4. HIV-related maternal mortality: Tuberculosis, malaria, and pneumonia

Nonpregnancy related infections, particularly tuberculosis, malaria, and pneumonia, are important causes of maternal death in HIV-infected pregnant or postpartum women. There are physiologic and immunologic changes in pregnancy that can alter susceptibility to and severity of infectious diseases. Pulmonary and cardiac physiologic changes may contribute to an increased risk of respiratory diseases, and a shift from cell-mediated immunity toward

humoral immunity during pregnancy may increase susceptibility to some infections [14]. Tuberculosis is a leading cause of maternal mortality in settings with a high HIV burden, and while the exact burden of HIV and tuberculosis co-infection in pregnant women is not known, several studies have demonstrated high HIV prevalence among maternal deaths attributed to tuberculosis. In a retrospective study in Zambia, 25% of maternal deaths were due to tuberculosis and 92% of these mothers were co-infected with HIV [15,16]. Co-infection with tuberculosis and HIV is particularly harmful in that HIV increases reactivation of tuberculosis and increases tuberculosis mortality, and the tuberculosis infection can cause a decrease in CD4 cells and an increase in viral replication [17]. Pregnant women infected with both tuberculosis and HIV have two to three times the risk of dying compared with pregnant women infected with tuberculosis alone [18,19]. Effective screening, prevention, and treatment measures exist for tuberculosis and can be accomplished during pregnancy if these activities are prioritized. Initiating active tuberculosis case-finding into existing prenatal clinics in Soweto, South Africa, through administration of a straightforward five-question screening tool led to discovery of a high burden of active tuberculosis among HIV-infected pregnant women [11]. Tuberculosis mortality among HIV-infected pregnant women can be prevented by integrating tuberculosis screening, isoniazid prophylactic treatment, tuberculosis treatment, and ART within prenatal care services [11].

Co-infection with HIV and malaria is also common in areas with a high prevalence of each of these diseases. HIV infection is associated with an increase in both the prevalence and severity of malaria, as well as an impaired response to malaria treatment [20]. The risks of severe anemia and maternal death in pregnant women co-infected with HIV and malaria are, respectively, three and five times those of pregnant women infected with malaria alone [21,22]. Established malaria prevention guidelines for pregnant women, including those with HIV co-infection, call for daily co-trimoxazole or intermittent prevention therapy with sulfadoxine and pyrimethamine; however, these prevention strategies continue to face barriers, largely due to constraints on health system infrastructure, outreach ability, and human and financial resources, which perpetuate the risk of complications and death from co-infection [20,23].

Pneumonia is a leading cause of indirect maternal death among HIV-infected pregnant women, yet a limited understanding of the specific causes of pneumonia exists [8]. A likely combination of etiologies include community acquired pneumonia, *Pneumocystis jirovecii* pneumonia, tuberculosis, and respiratory failure of unknown etiology; yet specific pathogens are rarely reported in the literature, limiting development and implementation of cause-specific interventions [8].

5. Direct obstetric complications and HIV-related maternal mortality

While the majority of HIV-related maternal deaths are from indirect causes, there is evidence that women infected with HIV have an increased risk of death from some obstetric complications. Findings from several studies suggest an increased risk of development of and mortality from both puerperal sepsis, especially after cesarean delivery, and abortion-related sepsis. HIV infection was shown to be a major risk factor for mortality due to

puerperal sepsis and abortion-related sepsis in the 2005–2007 South African confidential enquiries report [8], and HIV-infected pregnant women have approximately six times the risk of developing puerperal sepsis and three times the risk of death from sepsis after delivery [8,24–26]. While data on the topic are limited, this risk is also seen in high-income countries despite wide access to and treatment with ART [27].

6. Effect of antiretroviral treatment on maternal mortality

While there has been an increase in the number of pregnant HIV-infected women who have access to and use ART in the past five years, there is a jarring lack of published data demonstrating the effect of ART on maternal mortality. In studies that do address the effects of ART on maternal survival, conclusions have been inconsistent. In an observational study that reviewed records of HIV-infected women receiving prenatal care in Malawi and Mozambique, ART for prevention of mother-to-child transmission reduced the maternal mortality ratio (MMR) 13-fold overall. Furthermore, the MMR showed a dose– response effect, with the lowest MMR among those women who received ART for more than 90 days [28]. However, the study did not compare the MMR for HIV-infected women with those who were uninfected; therefore it is not known if the risk was reduced to the general population level. In a recent systematic review addressing the contribution of HIV to pregnancy related death, no difference in the pooled relative risk of mortality was seen in HIV-infected pregnant or postpartum women in studies done during a time when ART was available compared with studies done in an era in which ART was not available [7,12]. However, as pointed out in that review, the studies varied by region and criteria for initiation of ART, limiting ART to women with very low CD4 counts. Most pregnant women would either not have had access to ART or received it only at the time of delivery. It is likely that the relative risk of death would be lower in treated pregnant women if all HIV-infected pregnant and postpartum women were on ART [7].

Despite improved access to ART in many countries in Sub-Saharan Africa over the past several years, including improved availability to pregnant women, most of the available published studies that report maternal deaths comprised women who had little or no exposure to ART, or the investigators were unaware of treatment status. While ART will certainly reduce HIV-related maternal deaths, the optimal timing of the initiation of treatment and the extent to which treatment will prevent mortality during pregnancy have not been determined.

7. Discussion and recommendations

There were an estimated 19 000–56 000 maternal deaths attributed to HIV-related causes in 2011, contributing to some 6%–20% of all maternal deaths worldwide. The contributors to these deaths are multifactorial and include infectious etiologies, complications of the pregnancy itself, contextual and structural barriers to care, and likely biological interactions that are not well understood. However, we do know that many of these deaths can be prevented with the implementation of high-quality obstetric care, prevention and treatment of common co-infections, and treatment of HIV with ART.

Identification and reduction of barriers to HIV testing and treatment in pregnancy, including stigma associated with HIV infection and the poor care that can result from this stigma, must be addressed as part of an overall strategy. Fully understanding the links among HIV infection, pregnancy, and stigma associated with HIV will be important to decrease the risk of untreated HIV disease and increased mortality. Access to early prenatal care, integration of prenatal, HIV, tuberculosis, and malaria care, and initiation of ART according to established WHO guidelines would improve availability of comprehensive pregnancy care and reduce maternal morbidity and mortality related to HIV in pregnancy.

Provision of good quality, evidence-based peripartum care and adherence to best surgical and infection prevention practices, including routine preoperative antibiotic prophylaxis, can reduce the direct obstetric complications caused by sepsis in HIV-infected and uninfected women. Where abortion is legal, education of women regarding the availability of safe services will save lives, and where safe abortion is not legally available, it is important to offer prompt, high-quality post-abortion care to save women's lives. Integration of family planning services into HIV care and both immediate and extended postpartum care will be key strategies to improve both maternal and infant survival, by limiting pregnancies to planned and wanted pregnancies and decreasing the opportunity for vertical transmission.

Improved maternal mortality surveillance systems, which include causes of death, HIV status, and ART status, will allow for a more complete understanding of the contribution of specific disease entities to maternal mortality in HIV-infected women, missed opportunities for testing and treatment, and the impact of ART treatment on maternal mortality reduction. To further address the many questions that remain, it will be important for the HIV and maternal health communities to converge and identify gaps in the collective understanding of HIV infection and maternal death. A research agenda could be created, and may include such questions as: what is the impact of ART on maternal mortality overall, and specifically on peripartum and postabortion sepsis? What is optimal, comprehensive care for HIV-infected women, and what are the best strategies for integrating HIV, tuberculosis, malaria, and family planning into prenatal and postnatal care? How does stigma manifest as a barrier to status disclosure and initiation and continuation of treatment, in particular in HIV-infected pregnant women? And finally, what are optimal testing, prophylaxis, and treatment strategies for women who have HIV co-infection with malaria and tuberculosis?

HIV-infected women are much more likely to die during or soon after pregnancy than their HIV-uninfected counterparts. These deaths are preventable through the provision of good quality prenatal care that includes ART and essential obstetric care. MDG 5 and the new call to eliminate preventable maternal mortality cannot be achieved unless we address the needs of HIV-infected women. These needs cannot be met without the development of a high-quality system of care for all women—a system that couples evidence-based best practices with emerging research findings, and incorporates political, community, and cultural will to value and prioritize the care of pregnant and post-partum women, including those infected with HIV.

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