The contribution of HIV to pregnancy-related mortality

Clara Calvert, Basia Zaba and Carine Ronsmans
London School of Hygiene and Tropical Medicine

Maternal Health and HIV: Examining Research through a Programmatic Lens
Harvard School of Public Health
10-11th June 2013
Background

All deaths in pregnant and postpartum (42 days) women

- Direct obstetric
- Indirect
- Coincidental

Maternal deaths

Pregnancy-related deaths

HIV -

HIV +

All deaths in pregnant and postpartum (42 days) women

Attributable to HIV/AIDS?
### HIV attribution: evidence from literature

**Empirical data:** Cause of death studies (verbal autopsy)

**Mathematical Model:** Institute of Health Metrics and Evaluation (IHME)

**Mathematical Model:** Maternal mortality Estimation Inter-Agency Group (MMEIG)

<table>
<thead>
<tr>
<th>HIV -</th>
<th>HIV +</th>
</tr>
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<tbody>
<tr>
<td>Direct obstetric</td>
<td></td>
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<td>Indirect</td>
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**HIV attributable**

<table>
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</tr>
</tbody>
</table>

- Direct obstetric: 50%
- Indirect: 100%
- Coincidental: 50%
HIV attribution: evidence from literature

Percentage of maternal deaths attributed to HIV/AIDS

Cause of death review 1997-2003

- Africa
- South Africa
- East Africa
- West Africa

IHME model

- South Africa
- East Africa
- West Africa

MMEIG Model

- South Africa
- East Africa
- West Africa
Why might there be excess mortality attributable to HIV in pregnancy?

HIV increases risk of obstetrical complications e.g. sepsis
HIV increases susceptibility/severity of conditions such as malaria/anaemia

Pregnancy-related immuno-suppression accelerates HIV disease progression

MORTALITY
Objectives

• To calculate the excess mortality attributable to HIV in pregnancy
  – Systematic review
  – ALPHA network data

• To establish whether HIV increases the risk of obstetric complications
  – Systematic review
  – ALPHA network data

• To establish whether pregnancy increases the risk of HIV progression
  – Systematic review
Objectives

• To calculate the excess mortality attributable to HIV in pregnancy
  – Systematic review
  – ALPHA network data

• To establish whether HIV increases the risk of obstetric complications
  – Systematic review
**Methods**

**HIV attribution: using relative risk and population attributable fraction comparing deaths rates in HIV+ and HIV- women**

<table>
<thead>
<tr>
<th>Relative Risk</th>
<th>Population Attributable Fraction</th>
</tr>
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<tbody>
<tr>
<td>HIV -</td>
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- Death rate in HIV+ pregnant and postpartum women
- Death rate in HIV-pregnant and postpartum women

**Death rate in all pregnant and postpartum women — death rate in HIV-pregnant and postpartum women**

HIV-attributable death does not necessarily mean an AIDS death
Methods

• **Search strategy**
  – PUBMED, EMBASE, POPLINE & AIM
  – Search terms: (maternal & HIV) & (mortality OR obstetric complication OR HIV progression)

• **Inclusion criteria**
  – At least 30 HIV-infected and HIV-uninfected women
  – HIV assigned using HIV testing
  – All countries and publication dates
  – Any language
Studies which report the risk of pregnancy related mortality in HIV-infected and HIV-uninfected women: **23** studies
### Results:

**pooled relative risk**

<table>
<thead>
<tr>
<th>Studies</th>
<th>RR (95% CI)</th>
<th>% Weight</th>
</tr>
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<tbody>
<tr>
<td>Black et al. 2009, South Africa</td>
<td>6.25 (3.65, 10.71)</td>
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<td>13.64 (0.84, 221.19)</td>
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<td>Khan et al. 2001, South Africa</td>
<td>7.21 (3.52, 14.74)</td>
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<td>Kourtis et al. 2006, USA</td>
<td>21.38 (15.43, 29.64)</td>
<td>11.43</td>
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<td>Kumar et al. 1995, India</td>
<td>19.25 (1.13, 327.84)</td>
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<td>Le Coeur et al. 2005, Republic of Congo</td>
<td>3.85 (1.69, 8.79)</td>
<td>7.67</td>
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<td>Lepage et al. 1991, Rwanda</td>
<td>0.33 (0.01, 8.17)</td>
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<td>3.01 (0.31, 28.79)</td>
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<td>8.89 (0.48, 164.36)</td>
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<td>Zvandasara et al. 2006, Zimbabwe</td>
<td>13.32 (8.67, 20.46)</td>
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Source: Calvert and Ronsmans (2013) AIDS
Results: pooled relative risk

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Source: Calvert and Ronsmans (2013) AIDS

Pooled Relative Risk: 7.74
95% CI: 5.37-11.16
Results: Population attributable fraction

$$PAF = \frac{prev \cdot (RR - 1)}{1 + prev \cdot (RR - 1)}$$

- West Africa: 6%
- East Africa: 17%
- Southern Africa: 53%
Objectives

• To calculate the excess mortality attributable to HIV in pregnancy
  – Systematic review
  – ALPHA network data

• To establish whether HIV increases the risk of obstetric complications
  – Systematic review
Effect of HIV infection on pregnancy-related mortality in sub-Saharan Africa: secondary analyses of pooled community-based data from the network for Analysing Longitudinal Population-based HIV/AIDS data on Africa (ALPHA)

Basia Zaba, Clara Calvert, Milly Marston, Raphael Isingo, Jessica Nakinyingi-Miiro, Tom Lutalo, Amelia Crampin, Laura Robertson, Kobus Herbst, Marie-Louise Newell, Jim Todd, Peter Byass, Ties Boerma, Carine Ronssmans

Summary

Background Model-based estimates of the global proportions of maternal deaths that are in HIV-infected women range from 7% to 21%, and the effects of HIV on the risk of maternal death is highly uncertain. We used longitudinal data from the Analysing Longitudinal Population-based HIV/AIDS data on Africa (ALPHA) network to estimate the excess mortality associated with HIV during pregnancy and the post-partum period in sub-Saharan Africa.

Methods The ALPHA network pooled data gathered between June, 1989 and April, 2012 in six community-based studies in eastern and southern Africa with HIV serological surveillance and verbal-autopsy reporting. Deaths occurring during pregnancy and up to 42 days post partum were defined as pregnancy related. Pregnant or post-partum person-years were calculated for HIV-infected and HIV-uninfected women, and HIV-infected to HIV-uninfected mortality rate ratios and HIV-attributable rates were compared between pregnant or post-partum women and women who were not pregnant or post partum.

Lancet 2013; 381: 1763-71
See Comment page 1899
London School of Hygiene & Tropical Medicine, London, UK (Prof B Zaba MSc, C Calvert MSc, M Marston MSc, A Crampin MD, J Todd MSc, Prof C Ronssmans PhD); National Institute for Medical Research, Tanzania, Mwanza, Tanzania (R Isingo MSc); MRC/UVRI Uganda Research Unit on AIDS, Entebbe, Uganda (J Nakinyingi-Miiro PhD); Rakai
Results: Mortality rates by HIV and pregnancy

Relative risk:
- Pregnant: 8.2
  (95% CI: 5.7-11.8)
- Not Pregnant: 20.5
  (95% CI: 18.9-22.4)

Attributable rate:
- Pregnant: 11.8 per 1,000 women years
- Not pregnant: 51.8 per 1,000 women years

Population attributable fraction:
- Pregnant: 44.6%
- Not Pregnant: 77.6%

Healthy pregnant woman effect?
Results: Mortality rates by HIV and pregnancy

Source: Zaba et al., (2013) Lancet

*PPP: Pregnant and postpartum
Objectives

• To calculate the excess mortality attributable to HIV in pregnancy
  – Systematic review
  – ALPHA network data

• To establish whether HIV increases the risk of obstetric complications
  – Systematic review
Methods

- Included studies which looked at incidence of obstetric complications by HIV status
  - Maternal haemorrhage
  - Hypertensive disorders of pregnancy
  - Dystocia
  - Sepsis
- Studies identified using the systematic review described previously
Results

- Included studies which looked at incidence of obstetric complications by HIV status: **44 studies**
  - Maternal haemorrhage: **17 data sets**
  - Hypertensive disorders of pregnancy: **19 data sets**
  - Dystocia: **5 data sets**
  - Sepsis: **25 data sets**
- Studies identified using the systematic review described previously
Results: Sepsis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Data Sets</th>
<th>I-squared (%)</th>
<th>p-value</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis (4 data sets)</td>
<td></td>
<td>9.4</td>
<td>0.346</td>
<td>3.43 (2.00, 5.85)</td>
</tr>
<tr>
<td>Endometritis (8 data sets)</td>
<td></td>
<td>19.6</td>
<td>0.274</td>
<td>2.51 (1.50, 4.21)</td>
</tr>
<tr>
<td>Caesarean - Sepsis (4 data sets)</td>
<td></td>
<td>0.0</td>
<td>0.925</td>
<td>5.81 (2.42, 13.97)</td>
</tr>
<tr>
<td>Caesarean - Wound infection (10 data sets)</td>
<td></td>
<td>30.1</td>
<td>0.168</td>
<td>1.75 (1.20, 2.55)</td>
</tr>
<tr>
<td>Caesarean - Endometritis (19 data sets)</td>
<td></td>
<td>47.0</td>
<td>0.036</td>
<td>1.86 (1.28, 2.71)</td>
</tr>
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Source: Calvert and Ronsmans, publication forthcoming
Summary

- **Cause of death review 1997-2003**
  - Africa
  - South Africa
  - East Africa
  - West Africa

- **IHME Model**
  - South Africa
  - East Africa
  - West Africa

- **MMEIG Model**
  - South Africa
  - East Africa
  - West Africa

- **Population attributable fraction**
  - Africa
  - South Africa
  - East Africa
  - West Africa

Percentage of maternal/pregnancy-related deaths attributed to HIV/AIDS

Maternal mortality

Pregnancy-related mortality
Summary

• A very high percentage and number of deaths to pregnant and postpartum women were attributable to HIV, but the % is smaller in pregnant than non-pregnant women

• Increased risk of maternal sepsis and endometritis in HIV-infected women will contribute to this excess mortality, although direct obstetric causes only likely to explain a tiny fraction of the excess mortality

• ART appears to decrease mortality in non-pregnant women, but not in pregnant women
Future plans

• Use the ALPHA network data to establish whether HIV increases the risk of obstetric complications

• Establish whether pregnancy increases the risk of HIV progression through a systematic review

• Investigate whether some types of ART and PMTCT programme are more successful in bringing down pregnancy-related mortality in HIV+ women
Thanks for listening!

Funders: Economic and Social Research Council, the Wellcome Trust and the Child Health Epidemiology Reference Group