

Causes of maternal death and impact of treatment:

What do we know?

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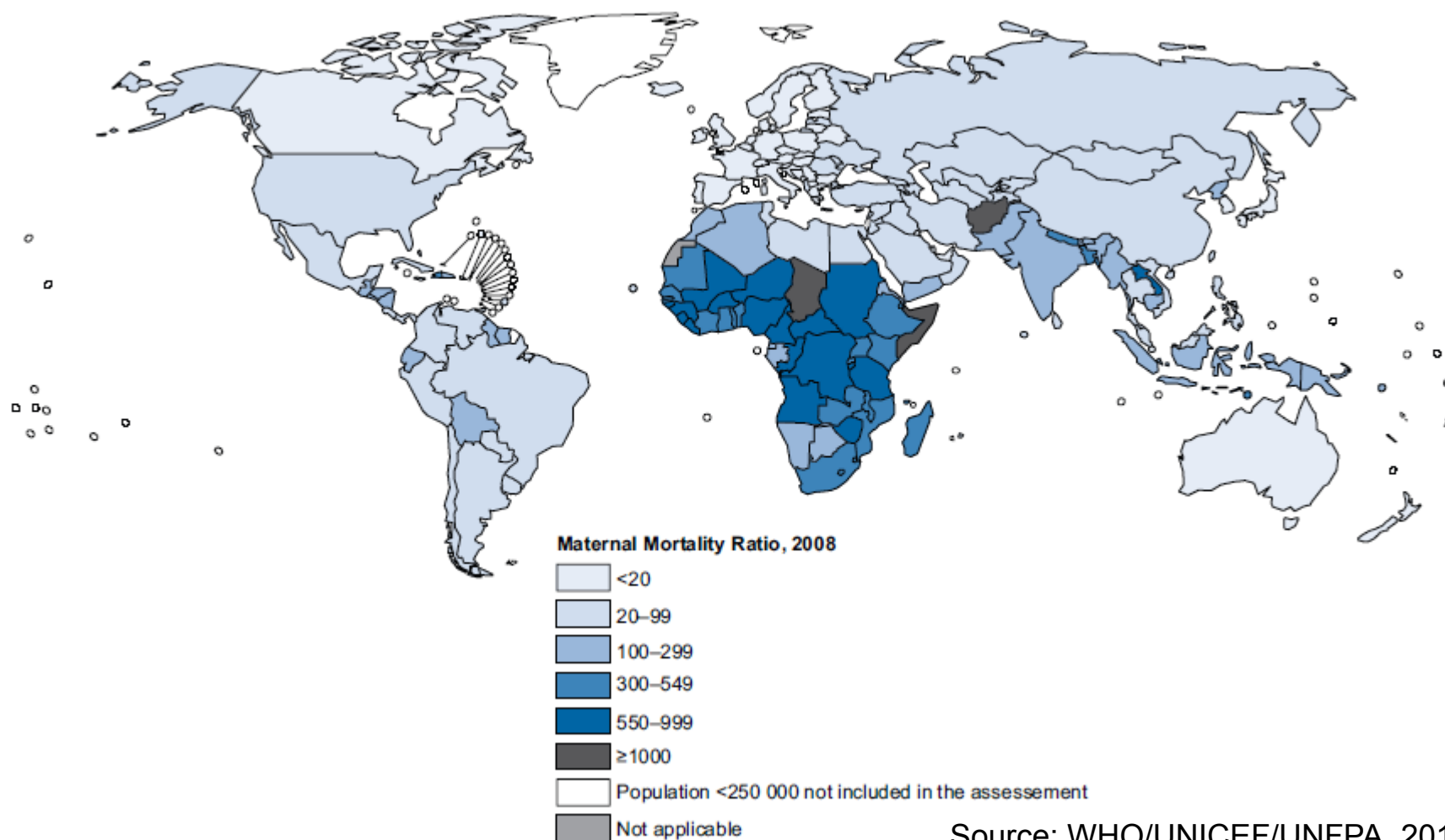
Division of Reproductive Health

Questions to be addressed today

- What do we know about the major causes of death among HIV+ women during pregnancy and post-partum?
- Do we know if pregnancy worsens HIV progression?
- What do we know about the impact of treatment?

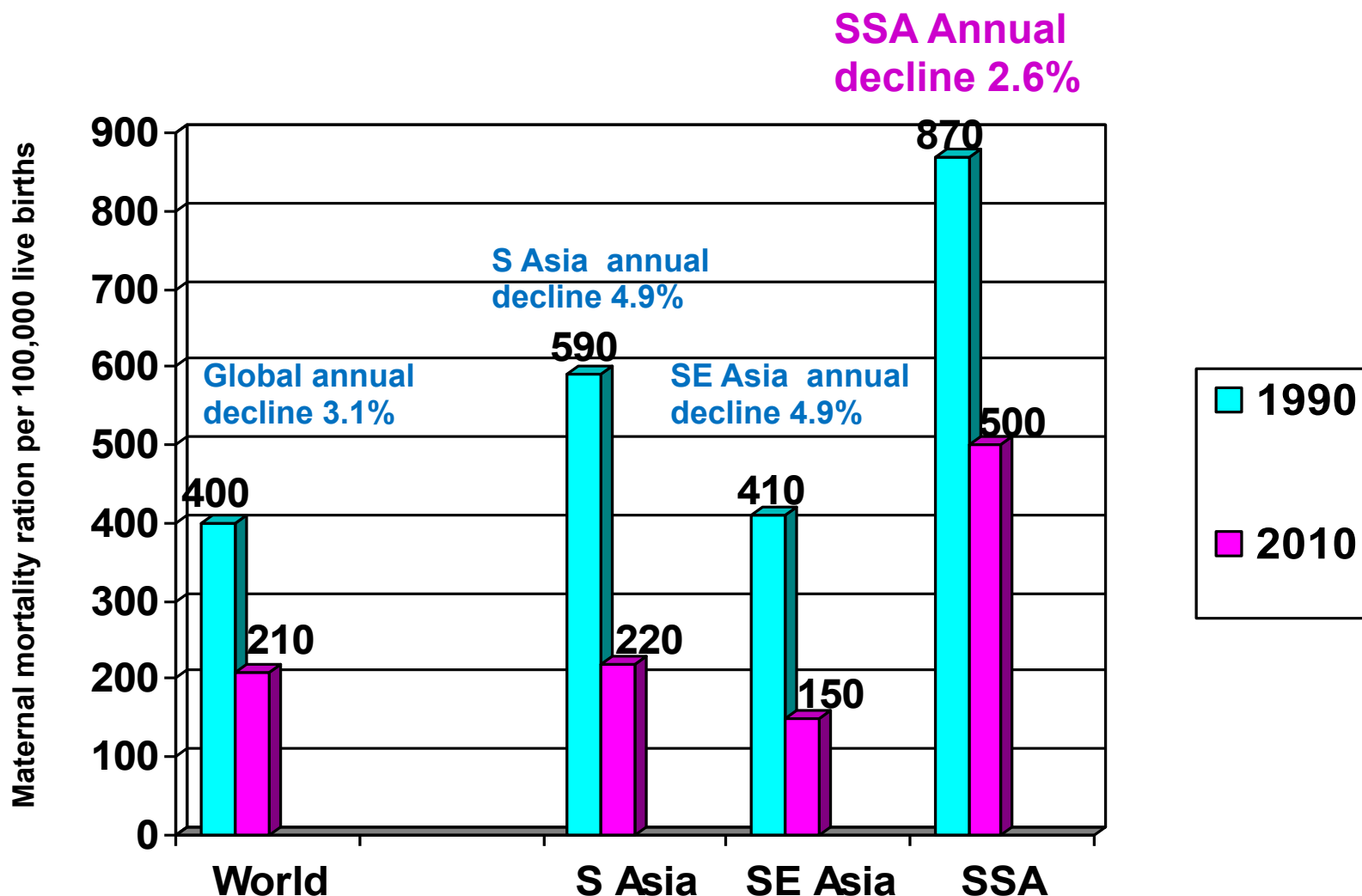
WHO, UNICEF, UNFPA, World Bank

Maternal mortality ratios by country 2008

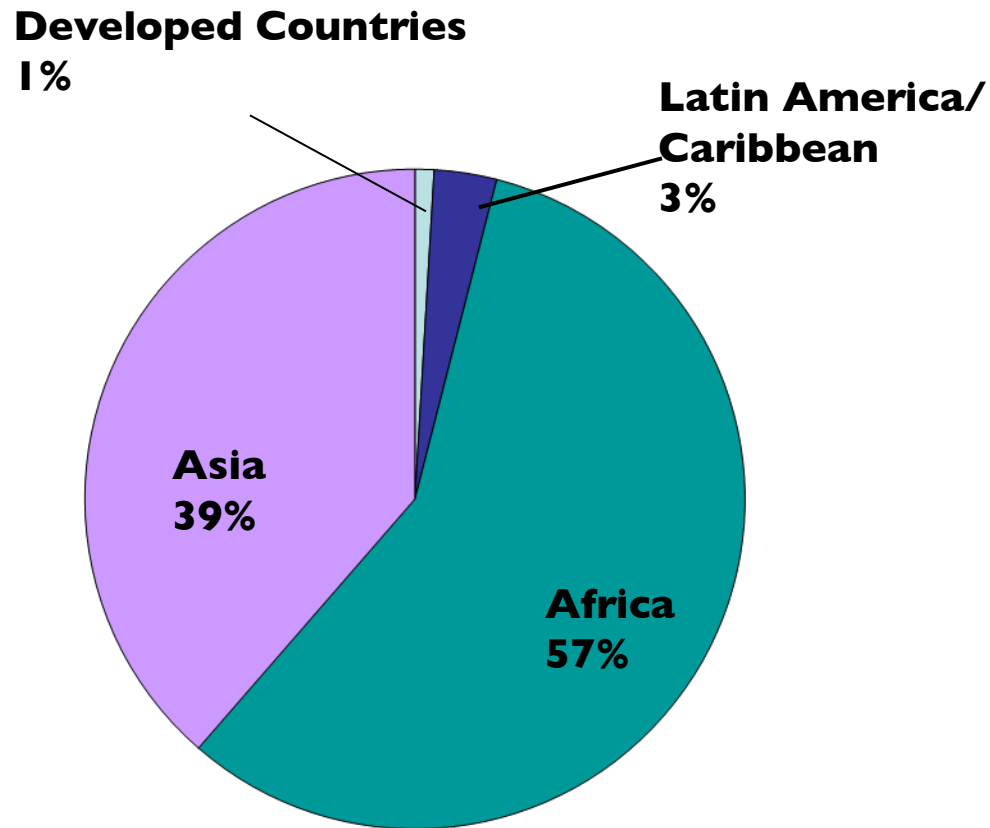


Source: WHO/UNICEF/UNFPA, 2010

Comparing global and SSA maternal mortality trends 1990-2010



Maternal Mortality in 2010



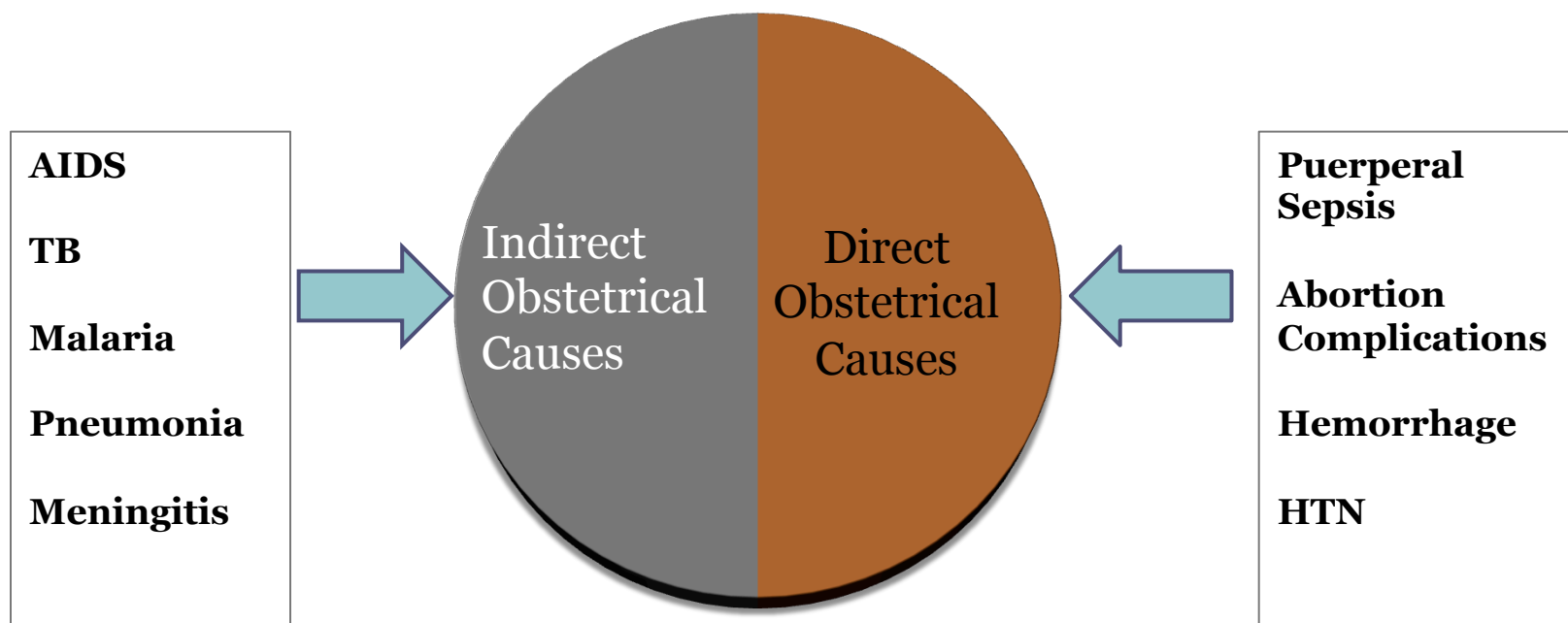
Total estimated deaths in 2010 = 287,000



Causes of mortality among HIV+ pregnant and post-partum women

Causes: Maternal Mortality and HIV

❑ Indirect infectious causes and direct obstetrical causes



Direct Obstetrical Complications

- Appears to be an increased risk of sepsis:
 - Puerperal sepsis, especially after C sections
 - Abortion related sepsis
- Uganda: post op wound infection of endometritis
RR 6.1 HIV infected /uninfected
- Malawi: increased maternal mortality from
peripartum infection OR 3.0 HIV infected/
uninfected
- US: increased risk of both pp endometritis and
sepsis $p < .001$, AOR for maternal death risk 11.3*

Perioperative complications of C-section in the USA according to HIV status, 1999-2002

Multicenter / Maternal-Fetal Medicine Units Network Cesarean registry (NICHD)
(19 academic medical centers)

Complication	HIV+ (N=378)	HIV- (N=54,281)	P	Adjusted OR (95% CI)
Endometritis	44 (11.6)	3,154 (5.8)	<0.001	1.9 (1.3-2.6)
Pneumonia	15 (4.0)	1,095 (2.0)	0.001	4.5 (1.8-11.0)
Maternal sepsis	8 (2.1)	692 (1.3)	<0.001	6.2 (2.3-17.0)
PP antibiotics	106 (28.0)	10,696 (19.7)	.007	1.4 (1.1-1.7)
ICU admission	7 (1.9)	427 (0.8)	.04	2.2 (1.0-4.7)
Maternal death	3 (0.8)	33 (0.1)	<0.001	11.8 (3.6-38.8)

Cause-specific mortality in pregnant and post-partum women¹

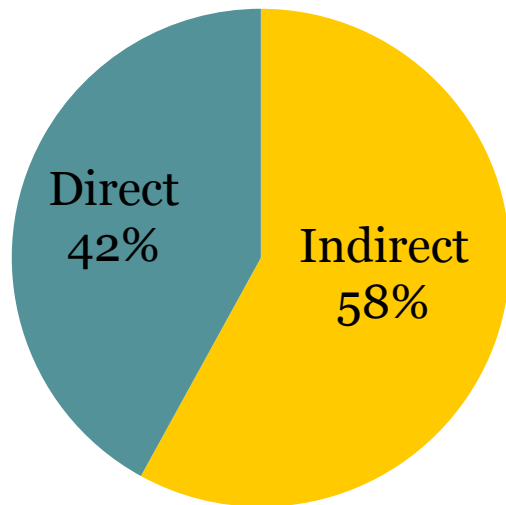
	Accidental deaths	Direct obstetric deaths	Causes not classified as direct obstetric		All causes
			AIDS	Other pregnancy-related	
HIV negative (41 deaths, 32,328 PYs ²)	0.03	0.56	-	0.68	1.27
HIV positive (51 deaths, 4,280 PYs ²)	-	0.94	7.01	3.97	11.92
rate ratio HIV+ / HIV-	-	1.7	-	5.8	9.4
95% CI for rate ratio	-	0.6-5.0	-	3.1-11.0	6.2-14.2

1 excluding Rakai: Verbal Autopsy cannot identify AIDS deaths

2 PA pro-rated to represent proportion with Verbal Autopsy data

Causes of maternal mortality

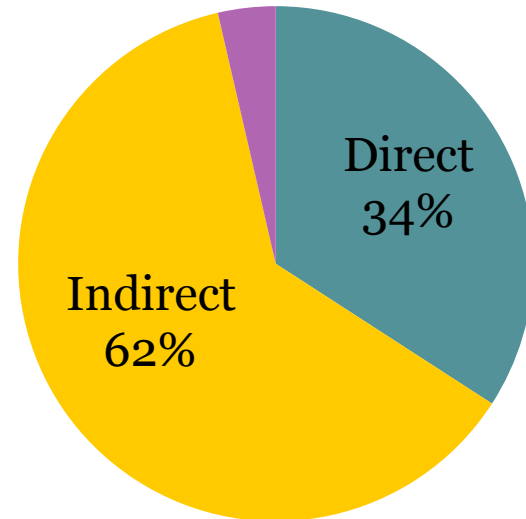
Lusaka, Zambia, 1996-97



Indirect deaths:

Malaria – 30%
TB – 25%
Pneum / other resp – 22%
AIDS – 9%
Cerebral inf – 4%
Other – 11%

Kisumu, Kenya 2003-08



Indirect deaths:

AIDS – 45%
Malaria – 13%
TB – 10%
Resp and cerebral inf – 8%
Other – 15%

Trends in maternal mortality due to specific causes at UTH, Lusaka, Zambia recorded over the past two decades

Study period	1974-1976	1982-1983	1989	1996-97
Total # of deaths	80	60	101	251
MMR	160	118	667	921
Direct causes (%)				
Abortion				
PIH	8	23	24	14
Hemorrhage	25	20	12	9
Sepsis	15	10	7	5
Ruptured uterus	17	15	15	8
Others	14	7	3	2
Total	15	5	9	4
	94	80	70	43
Indirect causes (%)				
Malaria	0	5	13	17
TB	0	0	2	14
Others	6	15	15	26
Total	6	20	30	57

Causes of death among HIV-infected pregnant women in selected countries

Cause of death	Percent of deaths South Africa 2005-2007	Percent of deaths Nigeria 2005-2009
<u>Indirect</u>		
Tuberculosis	8	16
Malaria	-	-
Pneumonia	12	11
Cerebral infections	3	22
AIDS	48	8
Other	2	5
Total	72	62
<u>Direct</u>	28	38

Indirect Infectious Deaths: Co-infection with TB

- ❑ **A leading cause of maternal mortality in settings with a high HIV burden (eg 25% of maternal deaths in Zambia, 1999)**
- ❑ **High HIV prevalence among maternal deaths attributed to TB**
- ❑ **Effect of co-infection**
 - HIV increases reactivation of TB and TB mortality
 - TB causes a CD4 drop and an increase in viral replication
 - Pregnancy does not appear to increase the risk of TB disease in HIV infected or uninfected women
 - But TB (and HIV) are independent risk factors for maternal death
- ❑ **Maternal mortality with co-infection: RR 2-3**
- ❑ **TB screening, prophylaxis and treatment important to prevent maternal death**
- ❑ **Level of protection from INH is unclear among HIV+ women**
- ❑ **Requires integrated antenatal care**

Indirect Infectious Deaths: Co-infection with Malaria

- ❑ Important cause of maternal mortality in SSA
- ❑ HIV increases prevalence and severity of malaria
- ❑ Co-infection common in high prevalence areas for both diseases
- ❑ Increased risk of severe anemia: OR 2-3
- ❑ Increased risk of maternal death: OR 5.0
- ❑ Key: malaria prophylaxis with daily cotrimoxazole or intermittent preventive treatment with Fansidar (drug interactions an issue and impact on HIV+ women unclear)
- ❑ Requires integrated antenatal care

Pneumonia

- ❑ **A leading cause of indirect maternal death among HIV infected pregnant women**
- ❑ **Limited understanding of the specific causes of pneumonia**
- ❑ **Likely a combination of etiologies including:**
 - Community Acquired Pneumonia
 - Pneumocystis carinii Pneumonia (PCP)
 - TB
 - Respiratory failure

Co-infection with HBV

- Estimated that 5-7% of pregnant women are co-infected (small number of studies)
- Up to 25% will be Hepatitis B e antigen + contributing to rapid HBV progression
- Mortality is higher among HIV-HBV co-infected people in general – not known in pregnancy but likely to be higher.

Mental Health, Violence

- ❑ **High prevalence of PP depression in HIV infected women**
- ❑ **Depression: predictor of non-adherence, difficulty accessing ANC, associated with faster progression to AIDS**
- ❑ **IPV: higher among HIV infected pregnant women: OR 1.5-3.0**

Does pregnancy impact HIV progression?

❑ **Limited findings from SSA**

- French and Brocklehurst (1998; Coite d'Ivoire)
 - ZDV at 36 wks or single dose NVP
 - Pregnancy has minimal impact
 - Limited by lack of control group

❑ **Saada (2000; France)**

- Compared pregnant and non-pregnant women with known date of seroconversion
- No association with HIV progression
- Selection bias due to healthy pregnancy effect an issue

❑ **Van Benthem (Europe; 2002)**

- Different ART regimens
- No statistical difference in ART progression between pregnant and non-pregnant women

❑ **Van d Paul (2007; rural Uganda)**

- Followed 109 WRA with known date of seroconversion and 30 HIV+ women with unknown date
- Less than 50% became pregnant
- Women who became pregnant had higher CD4 at conception and steeper CD4 decline after pregnancy approaching that of women who never became pregnant –initial comparative immunological advantage was “lost as a result of pregnancy”
- No significant differences in median time to CD4 count <200, AIDS or death between women with zero, one or more pregnancies

HIV progression during pregnancy in women on HAART?

❑ **Minkoff (2003; US and PR) – single pregnancy vs repeat pregnancy; 4 treatment groups**

- Of all regimens, HAART raised CD4 percentages the most (by 2% in 6 months)
 - Caveat: small number of women on HAART
- Women with a second pregnancy had a lower risk of death and no significant effects on HIV disease progression
 - ?healthy pregnancy effect?
- Need for more comprehensive understanding of the interaction between progression of HIV, pregnancy and HAART

❑ **Martin (2006; London)**

- Progression to AIDS is infrequent
- No matched cohort of HIV+ non-pregnant women or women not on treatment

❑ **Tai (2007; US) – observational cohort**

- Matched pair analysis of pregnant with non-pregnant women
- 75% on HAART
- 8% of pregnant women progressed to Class C event or death compared with 24% of non-pregnant women
- healthy pregnancy effect not accounted for

Does pregnancy impact HIV progression?

- ❑ **Studies have limitations related to**
 - Lack of control group
 - Healthy pregnancy effect - selection bias difficult to adjust for
- ❑ **Nevertheless, conclusions so far are that pregnancy does not appear to accelerate HIV disease progression**
- ❑ **No evidence of increased risk of death from AIDS in pregnant vs. non-pregnant HIV infected women**

Antenatal ART and pregnancy outcomes

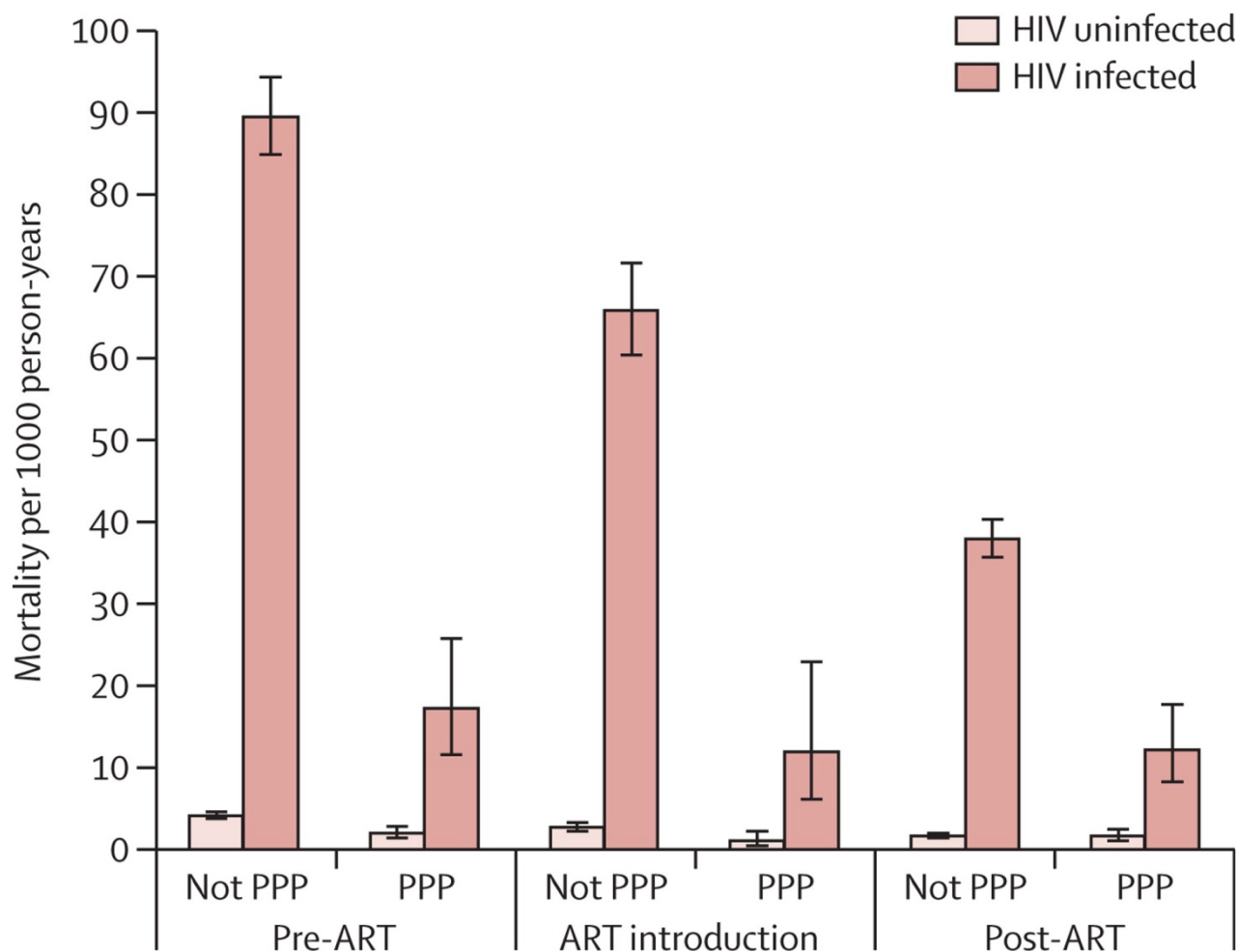
(Retrospective cohort study in Malawi and Mozambique)

Days of antenatal triple ART	Maternal mortality N (%)	Abortion / stillbirth N (%)	Prematurity N (%)
No ART	5/68 (7.4)	18/68 (26.5)	7/10 (70)
0-30	10/365 (2.7)	26/365 (7.1)	121/215 (56.3)
31-90	17/1470 (1.2)	57/1470 (3.9)	319/1386 (23.0)
>90	10/1370 (0.7)	68/1370 (5.0)	113/1330 (8.5)
Total	42/3231 (1.3)	169/3273 (5.2)	560/2941 (19.0)
P	<0.001	<0.001	<0.001

- Significant dose effect
- But still extraordinarily bad outcomes even in > 90 day group
- Need to compare with HIV- women to understand risk

Mortality rates in HIV-infected and HIV-uninfected women, by pregnancy status and availability of ART

Pooled Analysing Longitudinal Population-based HIV/AIDS data on Africa (ALPHA) network data, 1990—2012.



Source: [The Lancet 2013; 381:1763-1771](#); DOI:10.1016/S0140-6736(13)60803-X (Zaba B et.al.)



Summary

- Risk of mortality 2-10 x higher among HIV-infected pregnant women
- Increased mortality risk primarily due to indirect causes (TB, malaria, pneumonia, cerebral infections and HIV) as well as infections particularly post-C-section and post-abortion
- No evidence of increased HIV progression during pregnancy but questions remain, particularly in developing countries
- ART removed risk in developed countries but numbers are small
- To be seen whether in developing countries ART will bring mortality rates down to the level of HIV-negative women
- Data quality, completeness / representativeness an issue

Programmatic implications

- More ART and sooner during pregnancy – requires increased HIV testing during earlier ANC for all women
- Integrated antenatal care – HIV, malaria, TB screening, prevention and treatment
- Barriers to care – stigma, adherence, continuum of care
- Prevention and treatment of post-abortion and post-C-section infections
- ART continued post-partum and beyond - Option B+ - issues include retention and adherence
- Screening for depression and IPV
- Better routine and research data on maternal morbidity and mortality among HIV-infected (and all!) pregnant and post-partum women
 - Maternal death surveillance and response
 - Pregnancy outcomes including data to assess treatment and outcomes of HIV-infected women

Research issues

- Impact of ART on maternal and pregnancy outcomes in developing countries
- Complications of ART
- Impact of TB and malaria prophylaxis / treatment during pregnancy in HIV+ women
- Drug interactions
- Causes of pneumonia mortality and its prevention
- Implementation of an integrated antenatal care package
- Prevention of post-Cesarean sepsis
- HIV progression – still outstanding questions related to healthy pregnancy effect
- Barriers to care
- Improved routine M&E

Thank-you



Definitions

Maternal death is defined as the death of a woman while pregnant or within 42 days of the termination of pregnancy irrespective of the duration and site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management but not from accidental or incidental causes. (ICD-9, ICD-10)

Direct obstetric deaths are maternal deaths resulting from obstetric complications of the pregnancy state, (pregnancy, labour or puerperium), from interventions, omissions or incorrect treatment, or from a chain of events resulting from any of the above.

Indirect obstetric deaths are maternal deaths resulting from previously-existing disease or disease that developed during pregnancy and which was not due to direct obstetric causes, but which was aggravated by the physiological effects of pregnancy

Pregnancy-related death is defined as all deaths of women during or within 42 days of pregnancy regardless of cause. (ICD-10 [58]). This term is useful for two main reasons:

Cause of death can be difficult to determine.

In developing countries, a high percentage of deaths that occur during pregnancy and the postpartum period is due to the pregnancy and its complications.

Late maternal death is defined as a maternal death due to pregnancy (direct or indirect obstetric causes) which occurred more than 42 days but less than one year after the end of pregnancy. (ICD-10 [58]) Some recent surveys show the importance of assessing maternal mortality during this year after birth, when severe complication occurred. However, late maternal deaths are not included in the maternal mortality ratio.