Mother to child transmission of TB: what do we know?

Amita Gupta MD MHS
Assistant Professor and Deputy Director
Center for Clinical Global Health Education (CCGHE)
Division of Infectious Diseases
Johns Hopkins University School of Medicine
BJ Medical College Clinical Trials Unit, Pune, India
agupta25@jhmi.edu

Catalysing HIV/TB Research: innovation, funding and networking.
Cape Town, South Africa July 19, 2009
Overview

• Global burden and epidemiology
• Impact on maternal-child health outcomes
• Screening for LTBI and active TB in pregnancy
• Treatment issues in Pregnancy
• Research Gaps
TB is a leading killer of women

- Single biggest killer of young women (15-44 years)
- More women die each year of TB than of all maternal mortality causes combined
- Over 900 million women TB-infected, one million will die, and 2.5 million will get sick annually
- Accounts for 9% of deaths among women 15 – 44 y.o., compared with war (4%), HIV (3%) and heart disease (3%)

*TB Advocacy, A Practical Guide 1999, WHO Global Tuberculosis Programme*
TB and HIV in women

- TB is the most common HIV-1 related illness and cause of mortality in women of reproductive age in Asia and Africa

- HIV and TB are independent risk factors for maternal mortality
  - TB-associated deaths in Zambia increased from 0% in 1970s to 14% in 1997

- Upto 15% of maternal deaths due to HIV/TB

TB has become a leading cause of maternal mortality

- Overall maternal mortality rate for the Durban hospital: 200 per 100,000 live births

<table>
<thead>
<tr>
<th>Maternal mortality rates</th>
<th>All</th>
<th>TB</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV+</td>
<td>323.3 per 100,000</td>
<td>12,170 per 100,000</td>
</tr>
<tr>
<td>HIV-</td>
<td>148.6 per 100,000</td>
<td>3,850 per 100,000</td>
</tr>
</tbody>
</table>

RR 3.2

Khan AIDS 2001
Maternal TB/HIV important risk factor for pediatric TB and mortality

• Estimated TB rate
  – 10 times higher in HIV-exposed uninfected children <5 years than in non-HIV exposed
  – 30 times higher in HIV-infected children < 5 years than non-HIV exposed (Mukade 1997)
  – 1596/100,000 pop. HIV+ infants ≤12 mo. vs 65.9/100,000 pop. in HIV-infants ≤12 mo (Hesseling CID 2009)

• Maternal TB/HIV important risk factor for pediatric TB and mortality (Pillay 2004; Khan 1999; Cotton 2008; Gupta 2007)
MTCT of TB

- **In utero**
  - Hematogenous dissemination via the umbilical vein
  - Aspiration/ingestion of infected amniotic fluid
- **Intrapartum**
  - Aspiration/ingestion of infected amniotic fluid or genital secretions
- **Postpartum**
  - Inhalation/ingestion of respiratory droplets from the mother
  - Ingestion of infected breast milk
## Risks from TB in pregnancy

<table>
<thead>
<tr>
<th>Risk</th>
<th>Rate per 100,000 pregnancies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
</tr>
<tr>
<td>Low birth weight (&lt;2.5kg)</td>
<td>16500</td>
</tr>
<tr>
<td>Prematurity (&lt;37wk)</td>
<td>11100</td>
</tr>
<tr>
<td>Small for dates</td>
<td>7900</td>
</tr>
<tr>
<td>Pre-eclampsia</td>
<td>4700</td>
</tr>
<tr>
<td>Vaginal bleeding</td>
<td>2200</td>
</tr>
<tr>
<td>Perinatal death</td>
<td>1600</td>
</tr>
<tr>
<td>Fetal death (16-28wk)</td>
<td>230</td>
</tr>
</tbody>
</table>

Very limited data on effect of TB disease during pregnancy in HIV-infected

_Bjerkedal 1975; Jana 1994; Bothamley 2001; Khan 2001; Figueroa-Damian R, 1998_
Obstetric Outcomes among Women with Extrapulmonary TB

<table>
<thead>
<tr>
<th>Event</th>
<th>Women with lymph node TB N=12</th>
<th>Women with ETB other N=21</th>
<th>Control women (N=132)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy-complications</td>
<td>3 (25)</td>
<td>7 (33)</td>
<td>24 (18)</td>
</tr>
<tr>
<td>Antenatal hospitalization</td>
<td>1 (8)</td>
<td>5 (24)</td>
<td>3 (2)*</td>
</tr>
<tr>
<td>Preterm labor</td>
<td>1 (8)</td>
<td>2 (10)</td>
<td>14 (11)</td>
</tr>
<tr>
<td>Acute fetal distress</td>
<td>0</td>
<td>4 (19)</td>
<td>10 (8)</td>
</tr>
<tr>
<td>Mode of delivery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-section</td>
<td>3 (25)</td>
<td>3 (14)</td>
<td>25 (19)</td>
</tr>
<tr>
<td>Forceps</td>
<td>0</td>
<td>3 (14)</td>
<td>8 (6)</td>
</tr>
<tr>
<td>SVD</td>
<td>9 (75)</td>
<td>15 (71)</td>
<td>99 (75)</td>
</tr>
</tbody>
</table>

Matched case control study

Jana NEJM 1999
## Perinatal Outcomes among Women with Extrapulmonary TB

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Women with lymph node TB N=12 (%)</th>
<th>Women with ETB other N=21 (%)</th>
<th>Control women N=132 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age, wk</td>
<td>38.9</td>
<td>38.6</td>
<td>38.8</td>
</tr>
<tr>
<td>Mean birth weight, g</td>
<td>2894</td>
<td>2617</td>
<td>2868*</td>
</tr>
<tr>
<td>Prematurity</td>
<td>1 (8)</td>
<td>2 (10)</td>
<td>10 (8)</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>1 (8)</td>
<td>7 (33)</td>
<td>14 (11)*</td>
</tr>
<tr>
<td>Apgar ≤6 at 1min</td>
<td>1 (8)</td>
<td>4 (19)</td>
<td>4(3)*</td>
</tr>
<tr>
<td>Congenital anomaly</td>
<td>0</td>
<td>0</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Perinatal death</td>
<td>0</td>
<td>2 (10)</td>
<td>2 (2)</td>
</tr>
</tbody>
</table>

*Jana NEJM 1999*
Vertical Transmission of TB/HIV

• Among 107 pregnant women with TB in Durban, 15% of neonates sampled in first 3 weeks of life had TB bacilli (Pillay CID 1999)

• Small studies suggest that TB in HIV+ pregnant women may increase risk of HIV in-utero transmission
  – 19% in-utero infection rate among 42 HIV/TB pregnant women compared to 5-10% in HIV

  Pillay Lancet ID 2004; DeCock 2000
Congenital TB

- Rare
- >176 cases reported in the literature
- Old data suggest prevalence <1% for offspring of untreated mothers (Hedvall 1953)
- Two possible routes of *M. TB* infection in utero are postulated:
  - **Hematogenous** infection through umbilical vein, with primary lesions in the liver and sometimes with porta hepatis lymphadenopathy;
  - **Prenatal aspiration** of infected fluid, with pulmonary and gastrointestinal disease predominating
Postpartum Tuberculosis Incidence and Mortality among HIV-Infected Women and Their Infants in Pune, India, 2002–2005

Anita Gupta, Uma Nayak, Malathi Ram, Ramesh Bhosale, Sandesh Patil, Anita Basavraj, Arjun Kakrani, Sheeja Philip, Dipali Desai, Jayagowri Sastry, and Robert C. Bollinger, for the Byramjee Jeejeebhoy Medical College–Johns Hopkins University Study Group

1Infectious Diseases, Johns Hopkins University School of Medicine, and 2Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; and 3Byramjee Jeejeebhoy Medical College and 4Byramjee Jeejeebhoy Medical College–Johns Hopkins University Maternal Infant Transmission Study, Pune, India

(See the editorial commentary by Mofenson and Laughon on pages 250–3)
## Characteristics of Cohort

715 women followed for 480.6 person-years

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>23 (18-35)</td>
</tr>
<tr>
<td>Married, n(%)</td>
<td>686 (96.8)</td>
</tr>
<tr>
<td>Less than 4&lt;sup&gt;th&lt;/sup&gt; grade education, n(%)</td>
<td>274 (38.6)</td>
</tr>
<tr>
<td>Employed outside home, n(%)</td>
<td>147 (20.6)</td>
</tr>
<tr>
<td>Median CD4 cell count, cells/mm&lt;sup&gt;3&lt;/sup&gt; (IQR)</td>
<td>465 (318-675)</td>
</tr>
<tr>
<td>Median HIV-1 viral load, copies/ml (IQR)</td>
<td>11,692 (2,302-48,187)</td>
</tr>
</tbody>
</table>
### Characteristics of Incident Post-Partum TB cases (N=24)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary TB</td>
<td>16 (66.7%)</td>
</tr>
<tr>
<td>Extra-pulmonary</td>
<td>6 (25%)</td>
</tr>
<tr>
<td>Both</td>
<td>2 (8.3%)</td>
</tr>
<tr>
<td>Median time to TB</td>
<td>3 months</td>
</tr>
<tr>
<td>Postpartum TB Incidence rate</td>
<td>5 per 100 PY (24 cases)</td>
</tr>
<tr>
<td>Baseline HIV-1 viral load &gt;50,000 copies/ml</td>
<td>11 (45.8%)</td>
</tr>
<tr>
<td>CD4 &gt;200 cells/mm3, n(%)</td>
<td>14 (62.5%)</td>
</tr>
</tbody>
</table>

Gupta CID 2007
## Postpartum Maternal TB incidence among HIV-infected women

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Incident TB N=24</th>
<th>No TB N=691</th>
<th>Adjusted Incidence Rate ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Employed Unemployed</td>
<td>10 (41.7)</td>
<td>137 (19.9)</td>
<td>3.00 (1.32-6.79) ref</td>
</tr>
<tr>
<td>CD4 &lt;200</td>
<td>9 (37.5)</td>
<td>41 (6.0)</td>
<td>7.58 (3.07-18.71) ref</td>
</tr>
<tr>
<td>CD4 ≥200</td>
<td>15 (62.5)</td>
<td>641 (94.0)</td>
<td></td>
</tr>
<tr>
<td>VL &gt;50,000</td>
<td>15 (62.5)</td>
<td>154 (22.7)</td>
<td>3.92 (1.69-9.11) Ref</td>
</tr>
<tr>
<td>VL ≤50,000</td>
<td>9 (37.5)</td>
<td>524 (77.3)</td>
<td></td>
</tr>
<tr>
<td>TST ≥ 5mm</td>
<td>9 (37.5)</td>
<td>136 (20.5)</td>
<td>3.08 (1.27-7.47) ref</td>
</tr>
<tr>
<td>TST &lt;5mm</td>
<td>15 (62.5)</td>
<td>529 (79.5)</td>
<td></td>
</tr>
</tbody>
</table>

Gupta CID 2007
Characteristics and outcomes of infants born to HIV-infected women, by maternal incident TB status

<table>
<thead>
<tr>
<th>Infant characteristic</th>
<th>No. of infants for whom data were available</th>
<th>Maternal TB status</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Incident active TB</td>
<td>No TB</td>
</tr>
<tr>
<td>Birth weight, median g (IQR)</td>
<td>704</td>
<td>2500 (2300–3000)</td>
<td>2600 (2400–2950)</td>
</tr>
<tr>
<td>Gestational age, median weeks (IQR)</td>
<td>706</td>
<td>38 (37–39)</td>
<td>38 (38–38)</td>
</tr>
<tr>
<td>Positive PCR results for HIV</td>
<td>709</td>
<td>9/24 (37.5)</td>
<td>62/685 (9.10)</td>
</tr>
<tr>
<td>Still birth</td>
<td>715</td>
<td>1/24 (4.17)</td>
<td>5/691 (0.72)</td>
</tr>
<tr>
<td>Breastfed</td>
<td>715</td>
<td>21/24 (87.5)</td>
<td>624/691 (90.3)</td>
</tr>
<tr>
<td>Duration of breastfeeding, median days (IQR)</td>
<td>715</td>
<td>105.5 (32.5–199.5)</td>
<td>100 (97–183)</td>
</tr>
</tbody>
</table>

Gupta CID 2007
Adjusted maternal and infant mortality rates within first year post-partum by maternal TB status

Maternal mortality adjusted for CD4, log viral load, hemoglobin, age, educational status. Infant mortality adjusted for HIV PCR status, preterm birth (<38 weeks), birth weight and maternal factors as above.

Maternal TB
- Mother: 0.9
- Infant: 8.5

No Maternal TB
- Mother: 0.4
- Infant: 2.5

aIRR 2.2 (0.6-3.8)  P=0.006
aIRR 3.3 (1.2-10.6)  P=0.02
Does pregnancy affect TB or TB/HIV disease progression?
Pregnancy and immune changes

- Systemic immunomodulation that simultaneously embraces cellular immunosuppression, immunotolerance to various antigens, and enhanced inflammatory response.

- Decrease in Th1/Th2 ratio and cytokines, especially in the 3rd trimester (favoring humoral)

- Increase in certain proinflammatory cytokines [e.g., interleukin-6 (IL-6), tumor necrosis factor], especially in the 2nd half of pregnancy

- Increase in the number of regulatory T cells

- Increase in asymmetrical IgG antibodies, which can bind antigen but are unable to activate effector function

- Increased expression of various activation-associated adhesion molecules on granulocytes and monocytes
Pregnancy-associated immune changes are biologically significant

- Pregnancy ameliorates the clinical course of multiple sclerosis and rheumatic arthritis
- Aggravates systemic lupus erythematosus
- Increased risk of infectious diseases, including measles, influenza and plasmodium falciparum malaria
- Impact on TB and HIV progression debated
  - Clinical data limited and are not consistent or convincing (Espinal 1992; Sterling 2007)
  - Recent pregnancy risk factor for TB in some studies

Research on optimal methods for early detection and prevention of TB in women needed
Screening pregnant women for active TB in low-income countries

• Key entry point for healthcare for women

• Opportunity to detect active and latent TB and educate women about TB, especially HIV-infected

• Active TB needs to be excluded prior to initiation of INH preventive therapy
FIGURE 2.11

Intensified TB case finding, diagnosis of TB and IPT provision among HIV-positive people, 2006. Numbers above bars show the number of people receiving the intervention as a percentage of estimated HIV-positive people in reporting countries. Numbers under bars represent the number of countries reporting data followed by the percentage of total estimated HIV-positive TB cases accounted for by reporting countries.
Screening and active TB prevalence among HIV-infected pregnant women

- Studies from South Africa have found a 2% prevalence among HIV-infected pregnant women screened in antepartum by symptom screen (Kali JAIDS 2006)

- 11% prevalence among tuberculin skin test (TST) positive South African HIV+ women assessed during post-natal follow-up (Nachega AIDS 2003)

- 1.4% prevalence among symptom screen or TST positive women assessed at around time of delivery in India (Gupta CROI 2008)

- Role of shielded chest radiograph and tuberculin skin testing in this population continues to be debated (Mosimaneotsile Lancet 2003; Kali JAIDS 2006; Gupta CROI 2008)
Comparison of the estimated mean fetal absorbed dose from various radiographic and computed tomographic (CT) procedures


Radiological Society of North America, 2007
Tuberculosis screening and case-finding around time of delivery

841 HIV+ women delivered

4 (0.4%) women had known TB prior to delivery

799 (95%) had TST placed and symptom screen

778 (97%) had TST read within 72 hours

199 (25%) had positive symptom screen or TST+
(164 (21%) TST+ and 41 (5%) Positive symptom screen)

11 (1%) Active TB

799 (99%) No active TB

Gupta CROI 2008
Tuberculosis screening and case-finding around time of delivery

- Among 576 with both negative TST and symptom screen, 3 (0.5%) cases of TB were diagnosed (NPV 99%; 95% CI 98.4-100).

- Of 223 eligible for CXR (positive TST and/or symptom screen), 145 (65%) had it within 2 weeks of TST, of which 26 (18%) had abnormal CXR.
  - Any CXR abnormality was found in 26 (18%)
  - Any abnormality compatible with active TB was found in 13 (9%)

- All our TB cases identified by either symptom screen or WHO staging
  - CXR did not rule in additional cases

- Smear or culture were not done on asymptomatic women

Gupta CROI 2008
Latent TB screening in pregnancy: TB skin test (TST)

- Immunological considerations suggest TST response might be reduced

- Studies in pre-HIV era found no difference in pregnancy (Montgomery 1968, Present 1075)
  - Limited by small numbers, retrospective design and inadequate controls

- HIV (Eriksen 1998, Mofenson 1995) mixed data
Predictive value of TST screening for post-partum incident TB

<table>
<thead>
<tr>
<th>Baseline (Delivery)</th>
<th>Incident TB +</th>
<th>No incident TB</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST+</td>
<td>9</td>
<td>136</td>
</tr>
<tr>
<td>TST-</td>
<td>15</td>
<td>528</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>664</td>
</tr>
</tbody>
</table>

Sensitivity = 37.5%
Specificity = 79.5%
Positive predictive value = 6.2%
Negative predictive value = 97.2%

Gupta CID 2007
Latent TB screening in pregnancy

• No data for IGRAs role

• Impact of pregnancy stage and TST/IGRA test characteristics unexplored
  – HIV
  – Malnutrition
INH preventive therapy

- Active screening and detection of TB especially in early post-partum period in PMTCT programs needed

- Use of INH may be helpful in mitigating negative consequences of HIV and latent TB co-infection among mothers and their infants
INH safety in pregnancy and post-partum

- **Animal Studies**
  - Increased rate of growth retardation in rats thought to be due to an insult in yolk sac blood vessel walls
  - No increase in malformations in mice, rabbits whose mothers received as much as 60 times the dose used in humans
  - Increase in skeletal malformations in rats at high doses
  - Chick embryo studies showed demyelination but B6 reversed these effects completely
  - One mouse study given 30 times human dose during pregnancy and lactation increased the frequency of pulmonary adenocarcinomas
  - Case-control in human children did not find this association

INH safety in pregnancy and post-partum

- Not teratogenic

- Association of INH and hemorrhagic disease in newborn suggested in one study but not confirmed in other reports (consider prophylactic vitamin K recommended at birth)

- **Hepatotoxicity**
  - Abnormal liver enzymes: 1-25%
  - Symptomatic liver disease 5.2 per 1000 patients in a study where 20,838 given INH for 12 mo.
  - 20 deaths in CA, 4 were in women who had started INH in pregnancy (Mouldings) – study criticized for weak methodology
  - Non-statistically significant increase in a study of Hispanic women
  - Risk factors: age, alcohol, underlying liver disease including chronic Hep B
  - Hepatotoxicity when combined with HAART in pregnancy unknown

- **Breastmilk**: safe. Concentration 1% up to 20%

  Snider; Francks 1988, Thompson Micromedex online
Antepartum vs postpartum INH for latent TB

- Boggess et al Ob Gyn 2000
  - Markov decision analysis model for +TST and negative CXR
  - Assumptions: INH started at 20 weeks gestation for 6 months
  - 67% efficacy
  - 20% compliance with complete course
  - .1% serious hepatitis

- Fewest cases occurred with antepartum treatment compared to postpartum or no treatment
TB APPRISE: IMPAACT P1078 with TBTC scientific input

- Randomized trial to assess safety and efficacy of INH initiated in antepartum to reduce maternal TB incidence and infant mortality

TB screening for active TB

No active TB Enrolled and randomized

Arm A: Standard of care + Active case finding + prenatal MVI

Arm B: Standard of care + Active case finding + prenatal MVI + INH/B6 to all women

Sample size n=1600, plan 144 week follow-up
TB APPRISE: IMPAACT P1078

• **1 endpoint:** time to incident TB in mother, rate of hepatotoxicity

- **Maternal**
  - TB prevalence in diverse ANC settings
  - INH Completion rates
  - Examine acetylator status and risk of hepatotoxicity
  - Predictive value of IGRAs in pregnancy and postpartum
  - INH resistance among culture confirmed cases

- **Infant**
  - TB-free survival
  - Assess impact on infant immune response to BCG
  - IGRA responses

• **Cost-effectiveness**
Treatment of TB in pregnancy

Safety and efficacy of new TB drugs?

Optimal treatment in pregnancy and post-partum women?

Drug-interactions and pharmacokinetic studies in HIV-infected women receiving HAART?
## First line drugs for TB in pregnancy

<table>
<thead>
<tr>
<th>Drug</th>
<th>FDA</th>
<th>Crosses placenta</th>
<th>Breast-feeding</th>
<th>Issues in HIV pregnant women</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH</td>
<td>C but Australia A</td>
<td>Yes</td>
<td>Yes</td>
<td>Hepatotoxicity esp Hep B, NVP</td>
</tr>
<tr>
<td>RIF</td>
<td>C</td>
<td>Yes</td>
<td>Yes</td>
<td>Drug interactions with NVP</td>
</tr>
<tr>
<td>EMB</td>
<td>B</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>PZA</td>
<td>C</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

A adequate well controlled studies; B animal studies no harm but inadequate human studies or animal studies show harm but human data do not; C animal studies show adverse effects and inadequate human data; D risk to fetus but use in life threatening situations may be warranted; X risk of fetal abnormalities AVOID

Brost Obstet Gyn Clin 1997; Bothamley Drug Safety 2001; Shin CID 2003; Micromedex
## Second line drugs for TB

<table>
<thead>
<tr>
<th>Drug</th>
<th>FDA</th>
<th>Crosses placenta</th>
<th>Breast-feeding</th>
<th>Issues in HIV pregnant women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strepto Mycin/ AGs</td>
<td>D</td>
<td>Yes</td>
<td>Likely Yes</td>
<td>ototoxicity</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>C</td>
<td>unk</td>
<td>No data</td>
<td></td>
</tr>
</tbody>
</table>

**FQs**

<table>
<thead>
<tr>
<th></th>
<th>FDA</th>
<th>Crosses placenta</th>
<th>Breast-feeding</th>
<th>Issues in HIV pregnant women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cipro</td>
<td>C</td>
<td>Yes</td>
<td>AAP Yes WHO No</td>
<td></td>
</tr>
<tr>
<td>Moxi</td>
<td>C</td>
<td>unk</td>
<td>unk</td>
<td></td>
</tr>
<tr>
<td>Cycloserine</td>
<td>C</td>
<td>yes</td>
<td>unk</td>
<td></td>
</tr>
</tbody>
</table>

**Italicics:** case reports of use in pregnancy

---

Brost Obstet Gyn Clin 1997; Bothamley Drug Safety 2001; Shin CID 2003; Micromedex online
### Other drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>FDA</th>
<th>Crosses placenta</th>
<th>Breast-feeding</th>
<th>Issues in HIV pregnant women</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMC 207</td>
<td>?</td>
<td>unk</td>
<td>unk</td>
<td>No data</td>
</tr>
<tr>
<td>Rifapentine</td>
<td>C</td>
<td>unk</td>
<td>unk</td>
<td>Teratogenic in rats/rabbits</td>
</tr>
<tr>
<td>Ethionamide</td>
<td>C</td>
<td>unk</td>
<td>unk</td>
<td>No data</td>
</tr>
<tr>
<td><em>Amoxicillin-clavulanate</em></td>
<td>B</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

**Issues in HIV pregnant women**

- Crosses placenta
- Breast-feeding
- No data
- Teratogenic in rats/rabbits

Italics: case reports of use in pregnancy

Brost Obstet Gyn Clin 1997; Bothamley Drug Safety 2001; Shin CID 2003; Micromedex online
MDR TB in pregnancy

- 18 published case reports (Gach 1999; Shin 2003; Nitta 1999; Lessnau 2003; Tabarsi 2007; Khan 2007;)
  - Only 1 case series describes 3 cases HIV+ (Khan 2007)
  - Afghanistan, South Africa, US
# MDR TB in pregnancy

<table>
<thead>
<tr>
<th>Nitta 1999 US</th>
<th>3</th>
<th>All</th>
<th>≥4</th>
<th>1 abort</th>
<th>2 FT</th>
<th>1 TST+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lossneau 2003 US</td>
<td>1</td>
<td>Yes</td>
<td>4</td>
<td>PT</td>
<td>cured</td>
<td>Child sep x2 yrs</td>
</tr>
<tr>
<td>Shin 2003 US</td>
<td>7</td>
<td>All (4yrs)</td>
<td>≥4</td>
<td>7 FT</td>
<td>6 cured</td>
<td>Healthy av.2.7 yrs</td>
</tr>
<tr>
<td>Tabrisi 2007 Afghan</td>
<td>1</td>
<td>Yes (2 yrs)</td>
<td>4</td>
<td>FT</td>
<td>Cured</td>
<td>Proph Healthy</td>
</tr>
<tr>
<td>Khan 2007 S. Africa</td>
<td>5 (3 HIV)</td>
<td>80% (7-15mo)</td>
<td>≥4</td>
<td>1 abort</td>
<td>1 lost</td>
<td>2/4 growth restricted</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3 FT,1PT</td>
<td>1 default</td>
<td>2/4 suspect TB</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>All cx+ at delivery</td>
<td>1 treated</td>
<td></td>
</tr>
</tbody>
</table>
Unanswered questions: research opportunities

• What are the best strategies for screening for latent TB in TB/HIV endemic areas?
  – Role of TST, IGRAs, sputum, CXR?

• What is the optimal timing for LTBI intervention? Antepartum vs postpartum?

• Safety, efficacy, cost-effectiveness of LTBI intervention using INH in pregnancy? Role of newer combinations?

• What are the best detection strategies for active TB in high risk pregnant women?
Unanswered questions: research opportunities

• What are the safety, tolerability, PK and drug interactions of new promising TB drugs in pregnant and nursing women?

• What impact will short courses of antiretroviral therapy in pregnancy have on maternal-child TB epidemiology?

• What impact will maternal INH preventive therapy + HIV antiretroviral therapy have on maternal-child outcomes?

• What are the key immunologic changes that occur during pregnancy that may affect TB risk, diagnosis, transmission and maternal TB vaccine strategies?
Ongoing and planned studies

- CDC-BOTUSA study - Botswana
- TB/PMTCT Study - Soweto
- TB APPRISE - IMPAAACT multicountry Africa/India
- TB in pregnancy outcomes study - Soweto
- Pk studies of TB/HIV drugs in pregnancy - South Africa and IMPAAACT
Recommendations

• TB screening should be integrated with PMTCT services.
• Research on maternal/perinatal TB is needed in high-burden settings.
• Healthcare workers need to be trained and given incentives to provide integrated TB/HIV services.
Botswana IPT Trial 2004-2009

Randomized Double-Blind Placebo Controlled Trial
2,000 participants- 1,000 per study arm

Healthy
HIV+ adult

6 mo INH qd → 30 mo placebo

36 mo INH qd

First 6 months: Open label INH.

72 % women enrolled. By April 2009, 268 pregnancies observed and ~50% of cohort were also receiving ART.
What is the purpose of the TB/PMTCT study?

• To measure how much TB there is among all pregnant women.

• To study the health of infants born to mothers with TB and/or HIV.

• To determine how best to implement TB screening in the PMTCT Clinics.
The TB/PMTCT Study Design

- 6 of 13 antenatal clinics in Soweto
  - Tertiary hospital-based
  - Large community health centers
  - Small primary health clinics

Phase I: Baseline
- Pregnant women
  - Symptom screen at time of first ANC visit
  - If positive then sputum for smear, Cx, DST

Phase II: Follow-up
- Mothers & Neonates
  - 4-6 weeks-old
  - Subset of HIV+/HIV- women with and without TB and their infants