Diagnosis and Treatment of TB in HIV-infected women

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Overview

- Global TB/HIV burden and epidemiology
  - Special case of pregnancy
- Screening and Diagnosis
  - Latent TB Infection (LTBI)
  - Active TB
- Treatment
  - LTBI
  - Active
Disclosures

• Receive funding
  – US National Institutes of Health (NIAID, NICHD)
  – Gilead Foundation
  – WHO
Burden of TB/HIV in women

TB
• 8.8 million new cases
• 59% Asia
• 26% Africa

HIV
• 2.6 million new cases
• 33 million prevalent cases
• 16% Asia
• 68% Africa

Women
– 3.2 million (36% of total)
– Deaths 0.32 million

Women
– 15.5 million (52% of total)
– Deaths 0.85 million

Highest burden in reproductive age 15-45 years of age

In areas high HIV prevalence, women in the 15-24 year age group have TB rates 1.5-2-fold higher than men.

male:female sex ratio in smear + TB cases by HIV epidemic level

WHO global TB Report 2009

DeLuca A et al. JAIDS 2009;50:196-9
TB, HIV and Fertility Rates in Sub-Saharan Reproductive Aged Women

- TB is most common HIV-related illness and cause of mortality in women of reproductive age in Asia/Africa, causing 700,000 deaths annually. (WHO Global TB control 2009).

- Peak TB case detection in women in Africa is in the early childbearing age group (25-34 years).

- In these same countries, the prevalence of HIV in women of childbearing age is higher than in men, HIV prevalence among TB cases is high, as is fertility.
Extrapulmonary TB more prevalent in women

- Being female identified as independent risk factor for EPTB

- US 253,299 cases, 73.6% were PTB and 18.7% were EPTB. Compared with PTB, EPTB was associated with female sex (OR 1.7; 95% CI, 1.7-1.8)

TB in HIV-infected pregnant and postpartum women: Impact maternal and infant outcomes
TB and HIV in women

• HIV and TB are independent risk factors for maternal morbidity and mortality
  – 3.2 x higher death in TB/HIV than TB alone in Durban


• TB/HIV in pregnancy
  – Both can be transmitted mother-to-child in utero, intrapartum, and postpartum
  – Maternal TB has negative consequences for
    • Mom: increased antenatal hospitalization, adverse pregnancy outcome (postpartum hemorrhage)
    • infant: increased prematurity, IUGR, low birth weight, mortality

Pillay IJTLD 2004; Pillay Lancet ID 2004; Jana NEJM 1999; Bjerkdal Scan J Resp Dis 1975; Lin IJOG 2010
Maternal TB/HIV important risk factor for pediatric TB and mortality

- Maternal TB/HIV increased risk of postpartum mortality by 2.2 fold and probability of infant death by 3.4 fold.


Sick mom=sick child
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
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CD4 cells (IQR)</strong></td>
<td></td>
</tr>
<tr>
<td>&gt;500</td>
<td>Ref</td>
</tr>
<tr>
<td>350-500</td>
<td>1.18 (0.63, 2.22)</td>
</tr>
<tr>
<td>&lt;350</td>
<td>2.20 (1.19, 3.48)*</td>
</tr>
<tr>
<td><strong>Viral load copies/ml</strong></td>
<td></td>
</tr>
<tr>
<td>≤ 3 log10</td>
<td>Ref</td>
</tr>
<tr>
<td>3-5 log10</td>
<td>3.67 (1.61, 8.32)</td>
</tr>
<tr>
<td>&gt; 5 log10</td>
<td>10.8 (4.25, 27.70)*</td>
</tr>
<tr>
<td><strong>Prepartum AZT</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>Ref</td>
</tr>
<tr>
<td>No</td>
<td>1.25 (0.76, 2.05)</td>
</tr>
<tr>
<td><strong>Single-dose NVP</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>Ref</td>
</tr>
<tr>
<td>No</td>
<td>1.25 (0.76, 2.70)</td>
</tr>
<tr>
<td><strong>Maternal HAART use</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>Ref</td>
</tr>
<tr>
<td>No</td>
<td>1.40 (0.50, 3.87)</td>
</tr>
<tr>
<td><strong>Maternal TB (prevalent or incident)</strong></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Ref</td>
</tr>
<tr>
<td>Yes</td>
<td>2.51 (1.05, 6.02)*</td>
</tr>
<tr>
<td><strong>Breastfeeding duration</strong></td>
<td></td>
</tr>
<tr>
<td>&lt; 4 months</td>
<td>Ref</td>
</tr>
<tr>
<td>&gt; 4 months</td>
<td>1.72 (1.70, 2.65)*</td>
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<tr>
<td><strong>Extended NVP</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>Ref</td>
</tr>
<tr>
<td>No</td>
<td>1.24 (0.79, 1.97)</td>
</tr>
</tbody>
</table>

Maternal TB associated with mother to child HIV transmission

783 HIV-infected Indian women
Followed median 365 days
33 cases TB
Median
Age 23 yrs
CD4 at delivery 472 cells/mm3

Gupta et al JID 2011
Screening and diagnosis: early detection and prevention of TB in women needed
Screening pregnant women for active TB in low-income countries

• Antenatal/PMTCT programs are 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 CID 2011)
- 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)
Screening Programs and Prevalence of Active TB in Pregnant HIV-Infected Women

- Soweto, South Africa (Kali PBN et al. JAIDS 2006;42:379-81): As part of post-HIV test counseling, HIV-infected pregnant women were given a 7 minute symptoms screen for TB by lay counselors; if symptomatic they were referred for further investigation.

- 370 women were screened, with symptoms of TB identified in 120 (32%).

- 8 women (2.2% of overall group, 7% of symptomatic group) were diagnosed with active TB, all smear-negative.
Screening Programs and Prevalence of Active TB in Pregnant HIV-Infected Women

- Johannesburg, South Africa (Nachega J et al. AIDS 2003;17:1398-400): TB screening with TST performed during postnatal follow-up for HIV-infected women and their male partners. If TST >5 mm, referred for work-up.

  - 11% of TST positive women were identified as having active TB.

  - Challenge: lack of return for TST results and lack of follow-up for TB evaluation.

28% did not return for result
24% did not have adequate TB evaluation

Courtesy of Lynne Mofenson, NIH
Screening of Pregnant women

- Soweto, South Africa *(Gounder JAIDS 2011)*
- Cross-sectional implementation study of integrating TB screening in 6 ANC/PMTCT clinics (3963 women, 37% HIV+)

**Symptom screen**
- cough ≥2 weeks, sputum production, fevers, night sweats, or weight loss performed during HIV pretest counseling by nurses
- If symptom positive, asked to provide a sputum for smear, culture, DST

**Symptom screen positive:**
- 23% HIV+ vs 14% HIV-
- 15 Active TB cases identified
- 10/1454 (0.6%; 688/100,000 persons) HIV+ vs 5/2483 (0.2%; 201/100,000 persons) HIV-
- (in addition, 6 smear-, MOTT Cx+)
New WHO Symptom Screen

- Any current cough, fever, night sweats or weight loss
- If yes, pursue further investigations for TB
- If no, consider IPT

- Meta-analysis: sensitivity 78%, specificity 50%, NPV 98% at 5% TB prevalence among HIV (90% if 20% TB prevalence)

(Getahun PLOS One 2011)
Tuberculosis screening and case-finding around time of delivery in HIV+ women

- HIV-infected Indian women participating in a clinical trial (SWEN) underwent symptom and TST screening at delivery, and underwent work-up if either was positive.
  - 11/841 women (1.4%) were diagnosed with active TB, (230 with positive symptom and/or TST screen, of which 187 received CXR; 107 of 130 met criteria for sputum and had it done)

### Table: Sensitivity, Specificity, PPV, NPV, Positive LR, Negative LR

<table>
<thead>
<tr>
<th>Screening criteria</th>
<th>Total population, %; Patients with advanced HIV disease, a, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity</td>
</tr>
<tr>
<td>WHO symptoms(^b) alone</td>
<td>54.5; 54.5</td>
</tr>
<tr>
<td>WHO symptoms or expanded criteria(^c)</td>
<td>63.6; 63.6</td>
</tr>
<tr>
<td>WHO symptoms or TST positivity(^d,e)</td>
<td>100; 100</td>
</tr>
<tr>
<td>WHO symptoms or abnormal chest radiograph</td>
<td>55.6; 55.6</td>
</tr>
<tr>
<td>WHO symptoms or TB-compatible chest radiograph(^f)</td>
<td>50.0; 50.0</td>
</tr>
<tr>
<td>WHO symptoms, expanded criteria, or abnormal chest radiograph</td>
<td>66.7; 66.7</td>
</tr>
<tr>
<td>WHO symptoms, expanded criteria, or TB-compatible chest radiograph</td>
<td>55.6; 55.6</td>
</tr>
</tbody>
</table>

NPV of new WHO recommended symptom screen (cough, fever, weight loss) alone NPV 99.3% (97.8% if CD4<350)

Gupta et al CID 2011
Cepheid GeneXpert
Game changer for diagnosis of active pulmonary TB

- Smear + 98-100%, Smear - 72-77%
- MTB/RIF sensitivity 94% **Not lower in HIV+**
- Median time to detection 0 days, 1 day for smear, 16 days liquid culture, 30 days solid culture
- Median time to treatment 5 days for smear - TB using MTB/RIF compared to 56 days
- Drug resistance line probe 20 days, conventional DST 106 days

Boehme Lancet 2011
A Model of TB Screening for Pregnant Women in Resource-Limited Settings Using Xpert MTB/RIF

Turnbull et al J Preg 2011
Latent TB screening, diagnosis and treatment
Why screen for latent TB

• Goal of Latent TB screening
  – Identify those at highest risk for reactivation disease
  – Target INH preventive therapy

• Implementation challenges
## Latent TB tests

<table>
<thead>
<tr>
<th>TST</th>
<th>IGRAs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pros</strong></td>
<td><strong>Pros</strong></td>
</tr>
<tr>
<td>- Inexpensive, low tech</td>
<td>- No return visit (result in 24 hrs)</td>
</tr>
<tr>
<td>- Been standard for decades</td>
<td>- No cross reactivity with BCG</td>
</tr>
<tr>
<td><strong>Cons</strong></td>
<td><strong>Cons</strong></td>
</tr>
<tr>
<td>- Requires return visit</td>
<td>- No booster effect</td>
</tr>
<tr>
<td>- Operator dependent (placement and reading)</td>
<td>- More likely positive in those recent MTB infection</td>
</tr>
<tr>
<td>- Cross reactivity/false positive</td>
<td>- Fresh blood sample needed</td>
</tr>
<tr>
<td>- Expensive, needs a lab</td>
<td>- Cutoffs and interpretation</td>
</tr>
</tbody>
</table>

Neither test can distinguish between active disease or latent TB infection. Both have false positives and false negatives and there is no gold standard.

*CDC MMWR 2010 Updated IGRA guidelines*
IGRAs in pregnancy

US data (Cohan, ACOG 2010 abstract)

Prospective cohort study of 199 pregnant women in CA. 22% TST+, 13.1% QGIT+
- 77% agreement (kappa=0.24)

International high burden

• Jonalgadda, JID 2010
  - TB ELSIPOT performed on archived PBMCs on 333 Kenyan HIV+ women
  - 43% positive, 4.5 fold increased rate of TB and 3.5 fold increased mortality
    - 16% indeterminant

• Mathad et al
  - Ongoing study of Indian pregnant women (IDSA 2011)

N=136 18% TST+, 34% QGIT+, 76% agreement (Kappa=0.4)
New WHO IPT Guidelines for HIV+ in high HIV/TB regions (December 2010)

1. Adults and adolescents living with HIV should be screened for TB with a clinical algorithm and those who do not report any one of the symptoms of current cough, fever, weight loss or night sweats are unlikely to have active TB and should be offered IPT.

   Strong recommendation, moderate quality of evidence

3. Adults and adolescents living with HIV who have an unknown or positive TST status and are unlikely to have active TB should receive at least six months of IPT as part of a comprehensive package of HIV care. IPT should be given to such individuals irrespective of the degree of immunosuppression, and also to those on ART, those who have previously been treated for TB and pregnant women.

   Strong recommendation, high quality of evidence
Latent TB prevalence varies among HIV+ women

- 30% in Tanzania where ANC HIV+ 5% (Sheriff BMC Infect Dis 2010)
- 49% in South Africa among HIV+, (Nachega AIDS 2003)
- 20% India among HIV+ where ANC HIV+ 2-3% (Gupta CID 2007)
- 11% in HIV+ in US (Mofenson Arch Int Med 1995)
Treatment as Prevention: The case for (latent) TB

IPT
HAART
HAART + IPT
Newer regimens
# Reduction in TB incidence

<table>
<thead>
<tr>
<th>Reduction in TB incidence</th>
<th>Study type</th>
<th>references</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IPT</strong></td>
<td>33% overall</td>
<td>12 trials</td>
</tr>
<tr>
<td></td>
<td>62% if TST+</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Akolo Cochrane meta-analysis</td>
</tr>
<tr>
<td><strong>HAART</strong></td>
<td>60-80%</td>
<td>4 observational studies</td>
</tr>
<tr>
<td><strong>HAART +IPT (not concurrent)</strong></td>
<td>76-89%</td>
<td>2 observational Cohort</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Golub AIDS 2007; AIDS 2009</td>
</tr>
<tr>
<td><strong>HAART+IPT</strong></td>
<td>50%</td>
<td>BOTUSA trial</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Zamandandi Lancet 2011</td>
</tr>
<tr>
<td><strong>HAART +IPT concurrent</strong></td>
<td></td>
<td>Ongoing trial</td>
</tr>
</tbody>
</table>
IPT and HAART in pregnancy

- Increased potential for hepatotoxicity
  - Pregnancy (Ouyang AIDS 2009)
  - HAART 0.5-9% grade 3 or higher (Ouyang AIDS 2009; AIDS 2010; Jamisse JAIDS 2007; Marazzi HIV Med 2006)
  - IPT (Mouldings 1989; Francks 1989)

Antepartum vs Postpartum INH

**Pros**
- More likely to prevent maternal and infant TB
- Compliance and follow-up may be better

**Cons**
- Potential increased toxicities for mother and fetus/infant when started in antepartum

EVIDENCE NEEDED TO CONVINCE PROVIDERS AND PROGRAMS
Prevention of TB in Pregnancy

- Pregnancy exclusion criteria for all IPT trials to date
- Randomized trial: to compare safety of immediate vs deferred (3 mos postpartum) INH in 950 pregnant HIV-infected women residing in HIV TB/HIV burden countries

TB Apprise: IMPAACT P1078

HIV-infected pregnant women: screen for active TB

No active TB, 14-34 weeks gestation, N=900 (f/u 48 weeks PP)

Arm A: Immediate INH during pregnancy
  • INH x 28 wks, then placebo until 40 wk PP

Arm B: Delayed INH, start 3 mos postpartum
  • Placebo until PP wk 12, then INH x 28 wks to 40 wk PP

Many women will be on HAART+IPT concurrently
2-10% may have occult HBsAg+
Assess effectiveness as secondary endpoint
Newer, shorter TB preventive regimens

- IPT for 6-9 months compliance varies 50-90%

- INH+ rifapentine weekly for 12 weeks as efficacious as 9 mo INH. CDC TBTC26 n=8000 but mostly US and only small number of HIV+ and not on HAART

- INH+rifapentine daily for 4 weeks ACTG 5279 n=3000 HIV+ persons ≥ 13 yrs, can be on NNRTI-based HAART

- PK,safety data for rifapentine in pregnancy needed
Treatment of active TB in women including during pregnancy

Timing of HAART?

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?
Some considerations

- Women may have more extrapulmonary TB
- Higher stigma, lower TB literacy, more delay in health seeking for symptoms (systematic review of 66 studies, submitted)
- Increased adherence to treatment
- Overall good treatment outcomes if seeks care for drug susceptible TB
# Key characteristics of trials of timing of ART during TB treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting</th>
<th>Key enrollment criteria</th>
<th>Median CD4 (IQR)</th>
<th>Primary endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CAMELIA</strong></td>
<td>Cambodia</td>
<td>Smear +, CD4 &lt; 200</td>
<td>25 (10 - 56)</td>
<td>Death</td>
</tr>
<tr>
<td>(Blanc, ANRS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>STRIDE</strong></td>
<td>Multi-national</td>
<td>Clinical TB, CD4 &lt; 250</td>
<td>77 (36 – 145)</td>
<td>AIDS or death</td>
</tr>
<tr>
<td>(Havlir, ACTG)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SAPIT</strong></td>
<td>South Africa</td>
<td>Smear +, CD4 &lt; 500</td>
<td>150 (77 – 254)</td>
<td>AIDS or death</td>
</tr>
<tr>
<td>(Abdool-Karim, CAPRISA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Effect of ART timing on death (CAMELIA) or death/AIDS (STRIDE, SAPIT)

Overall

- CAMELIA: 34% ↓ p=0.004
- STRIDE: 19% ↓ p=0.45
- SAPIT: 11% ↓ p=0.73

CD4 < 50 in STRIDE and SAPIT

- CAMELIA: 34% ↓ p=0.004
- STRIDE: 42% ↓ p=0.02
- SAPIT: 68% ↓ p=0.06

Timing of ART in patients with TB

• **Advanced AIDS (CD4 < 50):** immediate ART (within 2 weeks) improves survival
  – Markedly increased risk of immune reconstitution inflammatory syndrome (IRIS), including fatal IRIS
  – Overall survival benefit despite this

• **CD4 > 50:** early ART (~ 2 months) provides good balance of competing risks of death/AIDS vs. IRD

• Caveats
  – **CNS involvement** – no benefit to immediate therapy, and there may be increased risk* (Torok, CID, 2011)
Important Drug Interactions with Rifampin

- **NRTIs (AZT, 3TC, TDF, etc.)**
  - No significant interactions

- **NNRTIs (EFV, NVP)**
  - RIF decreases NVP exposure 40-50%, EFV 20-35% (but effects highly variable)

- **Protease inhibitors (LPV/r, DRV/r, ATV/r, etc.)**
  - RIF decreases exposure >80%, in most cases
  - Increasing the PI dose can lead to hepatotoxicity

- **CCR5 Inhibitors (Maraviroc)**
  - RIF reduces maravirocin exposure by 63%

- **Integrase inhibitors (RAL)**
  - RIF reduces raltegravir exposure by 40-60%

*Courtesy of Kelly Dooley, JHU*
What to Start in HIV+ woman

• EFV-based if not pregnant or in 1\textsuperscript{st} trimester
• NVP can be considered but avoid lead-in dose
• PI with rifabutin: limited data but new data suggest rifabutin should be dosed 150mg daily
• Double dosing PI with rifampin?
• Abacavir, 3TC, AZT
• Raltegravir based 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</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, PIs</td>
</tr>
<tr>
<td>rifabutin</td>
<td>B</td>
<td>Unk</td>
<td>unk</td>
<td>Drug interactions with PIs</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>Streptomycin/ AGs</td>
<td>D</td>
<td>Yes</td>
<td>Likely Yes</td>
<td>ototoxicity</td>
</tr>
<tr>
<td><em>Capreomycin</em></td>
<td>C</td>
<td>unk</td>
<td>No data</td>
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</table>

**FQs**

<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><em>Cipro</em></td>
<td>C</td>
<td>Yes</td>
<td>AAP Yes WHO No</td>
<td></td>
</tr>
<tr>
<td><em>Moxi</em></td>
<td>C</td>
<td>unk</td>
<td>unk</td>
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</tr>
<tr>
<td><em>Cycloserine</em></td>
<td>C</td>
<td>yes</td>
<td>unk</td>
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</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>
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</thead>
<tbody>
<tr>
<td>TMC 207</td>
<td>?</td>
<td>unk</td>
<td>unk</td>
<td>No data</td>
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<td>Rifapentine</td>
<td>C</td>
<td>unk</td>
<td>unk</td>
<td>Teratogenic in rats/rabbits</td>
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<tr>
<td>Ethionamide</td>
<td>C</td>
<td>unk</td>
<td>unk</td>
<td>No data</td>
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<tr>
<td>Amoxicillin-clavulanate</td>
<td>B</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

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

- 57 published case reports (Gach 1999; Shin 2003; Nitta 1999; Lessnau 2003; Tabarsi 2007; Khan 2007; Palacios 2009; Toro JAIDS 2011)
  - Only 3 case series describes 4 cases HIV+ (Khan 2007; Palacios 2009, Toro JAIDS 2011)
  - Afghanistan, South Africa, US, Peru
<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Age</th>
<th>Prior TB</th>
<th>Resistance</th>
<th>Maternal</th>
<th>Rx</th>
<th>Infant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitta 1999 US</td>
<td>3</td>
<td></td>
<td>All</td>
<td>≥4</td>
<td>1 abort</td>
<td>2 FT</td>
<td>1 TST+</td>
</tr>
<tr>
<td>Lossneau 2003 US</td>
<td>1</td>
<td>22</td>
<td>No</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>21</td>
<td>All</td>
<td>≥4</td>
<td>7 FT</td>
<td>6 cured</td>
<td>Healthy av.2.7 yrs</td>
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<td>5</td>
<td>26</td>
<td>Yes</td>
<td>≥4</td>
<td>1 abort</td>
<td>1 failed</td>
<td>2/4 growth restricted</td>
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<td>24.4</td>
<td>90%</td>
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<td>1 lost</td>
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Conclusions

• HIV-infected women of reproductive age at high risk for TB in sub-Saharan Africa and Asia
  – Impacts maternal and infant health

• Simple symptom screening tools have high negative predictive value but new paradigms to rule in TB are needed

• New paradigms for latent TB assessment needed

• Treatment studies for prevention and for active disease need to include pregnant and breastfeeding women