Diagnosis and Treatment of TB in HIV-infected women

Amita Gupta MD MHS
Associate Professor of Medicine and International Health
Center for Clinical Global Health Education
Johns Hopkins University
JHU-BJ Medical College Clinical Trials Unit, Pune, India
agupta25@jhmi.edu

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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

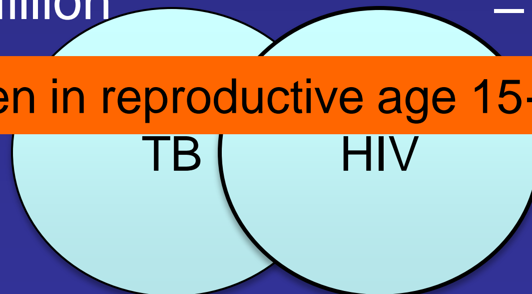
TB

- 8.8 million new cases
- 59% Asia
- 26% Africa
- Women
  - 3.2 million (36% of total)
  - Deaths 0.32 million

HIV

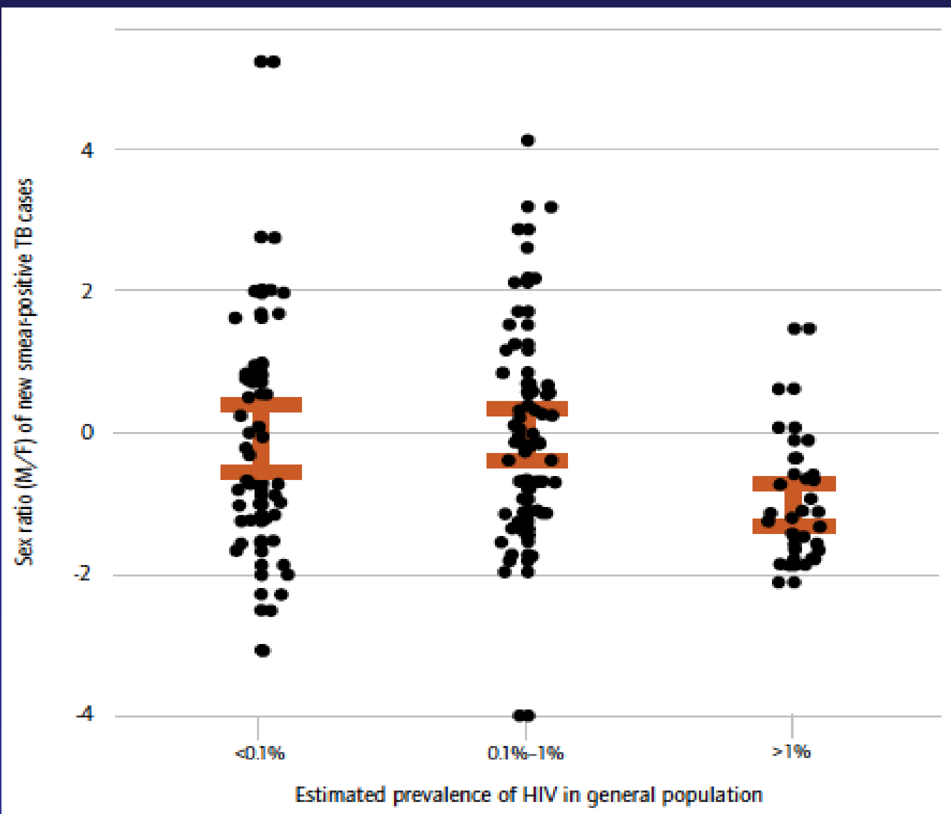
- 2.6 million new cases
- 33 million prevalent cases
- 16% Asia
- 68% Africa
- Women
  - 15.5 million (52% of total)
  - Deaths 0.85 million

Highest burden in reproductive age 15-45 years of age

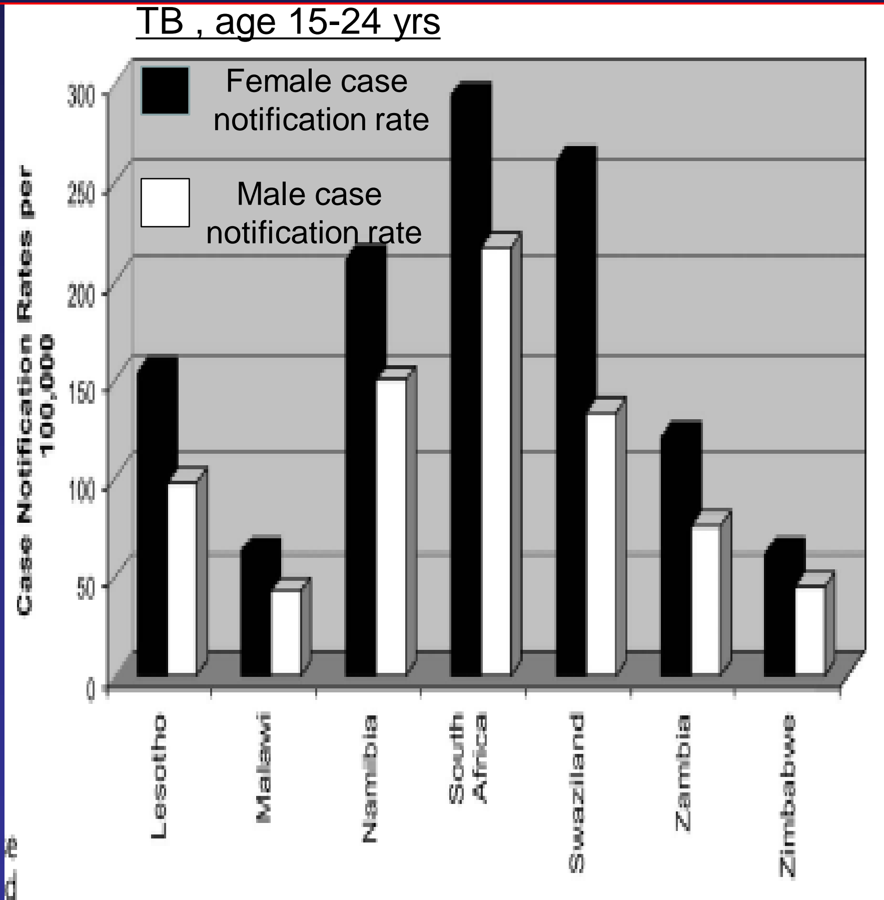


WHO Global TB Report 2011, UNAIDS Global AIDS Report 2011, WHO 2009 Women and Health

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

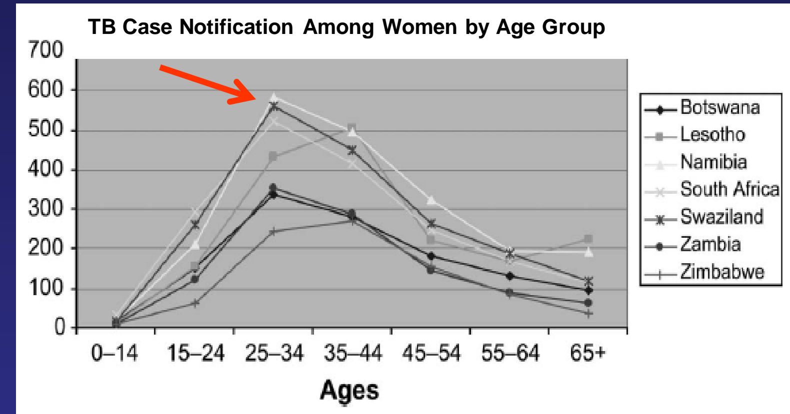


WHO global TB Report 2009

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.

TABLE 1. HIV Prevalence, Sex, Fertility, and HIV-Related TB in Selected African Countries[15,16]

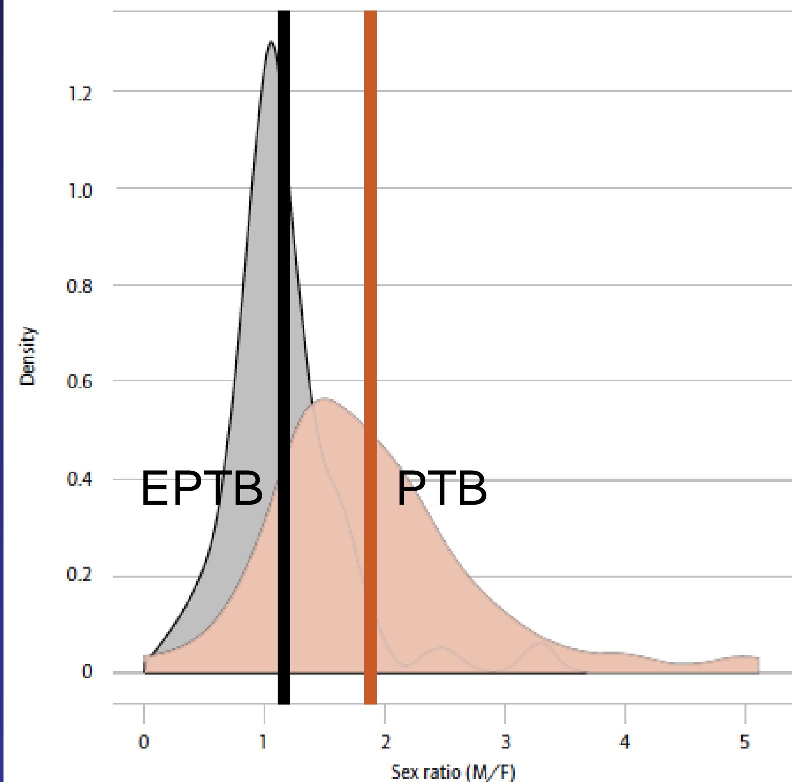
	HIV Prevalence in Women ≥15 Years of Age (% of Total)	Total Fertility Rate (Births per Woman)	HIV Prevalence in Incident TB Cases (Men and Women) (%)
Botswana	54	3.2	34
Malawi	59	6.0	70
Mozambique	60	5.5	30
South Africa	58	2.8	44
Swaziland	57	3.9	54
Zimbabwe	59	3.6	43

DeLuca A et al. JAIDS 2009;50:196-9

Slide Courtesy of Lynne Mofenson

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)



Lin IJTLD 2009; Yang CID 2004; Kingkaew IJID 2009; Lowieke EID 2006; WHO Global TB Report 2009

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

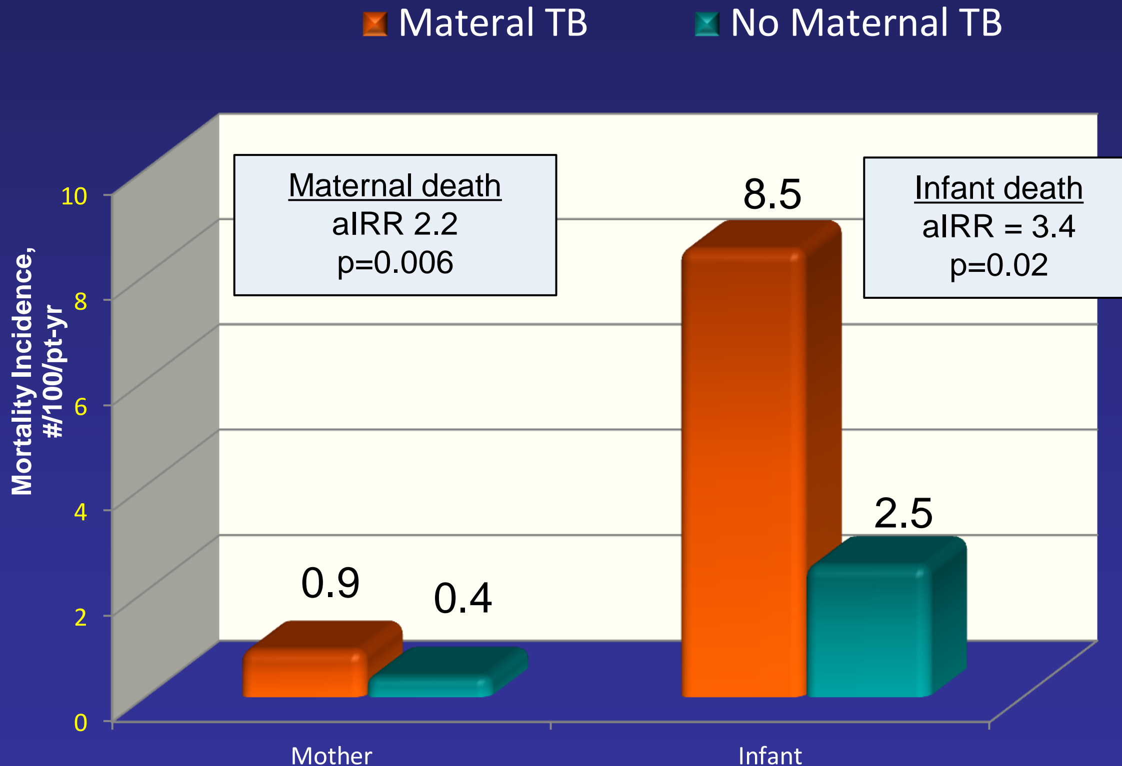
WHO Global TB report 2008; Khan AIDS 2001; Ahmed Int J Tub Lung Dis 1999; Mendendez PLOS One 2008

- 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.



715 HIV-infected pregnant women in Pune, India

TB incidence 5/100 pt-yr (24 of 715 HIV+ women)

Sick mom=sick child

Gupta A et al. Clin Infect Dis 2007;45:241-9

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

Maternal TB associated with mother to child HIV transmission

Characteristic	Adjusted OR (95% CI)
CD4 cells (IQR)	
>500	Ref
350-500	1.18 (0.63,2.22)
<350	2•20 (1•19,3.48)*
Viral load copies/ml	
≤ 3 log10	Ref
3-5 log10	3.67 (1.61, 8.32)
> 5 log10	10•8 (4•25, 27•70)*
Prepartum AZT	
Yes	Ref
No	1•25 (0•76, 2•05)
Single-dose NVP	
Yes	Ref
No	1•25 (0•76, 2•70)
Maternal HAART use	
Yes	Ref
No	1•40 (0•50, 3•87)
Maternal TB (prevalent or incident)	
No	**Ref**
Yes	**2•51 (1•05, 6•02)***
Breastfeeding duration	
< 4 months	Ref
> 4 months	1•72 (1•70, 2•65)*
Extended NVP	
Yes	Ref
No	1•24 (0•79, 1•97)

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*

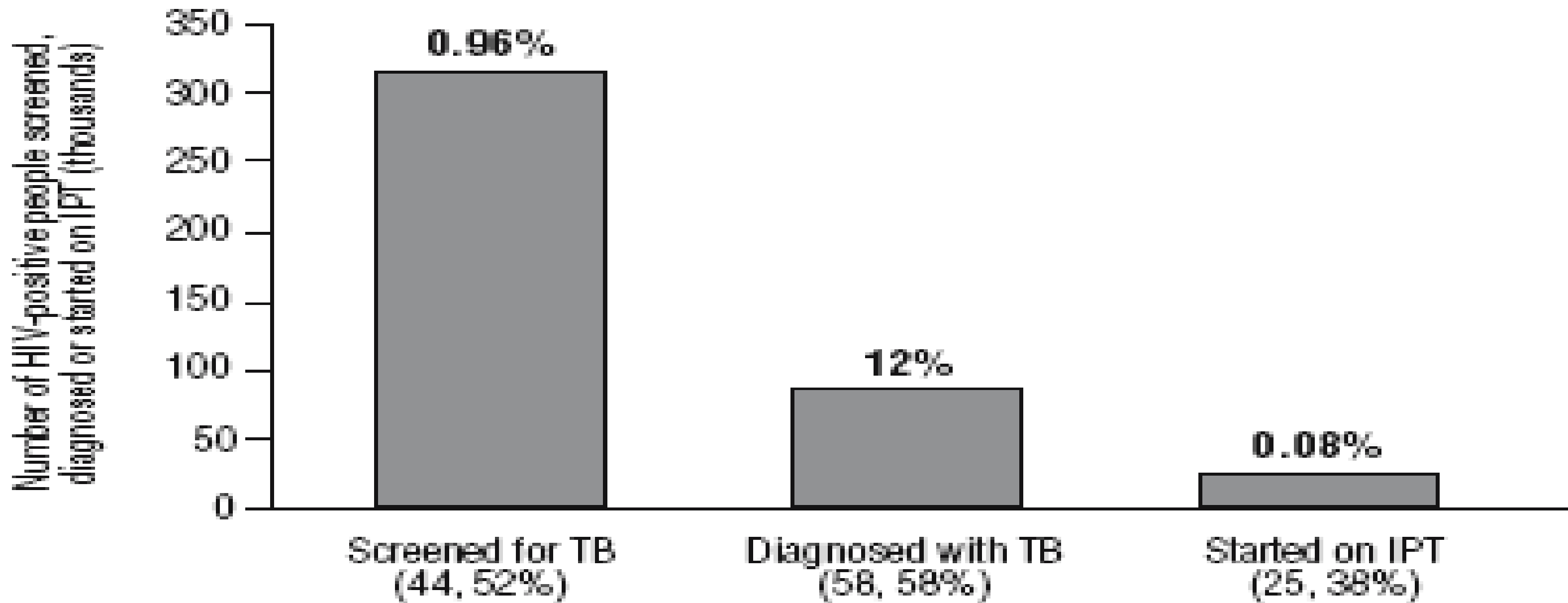
Screening and diagnosis: early detection and prevention of TB in women needed

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.



WHO 2008

Screening and active TB prevalence among HIV-infected pregnant women

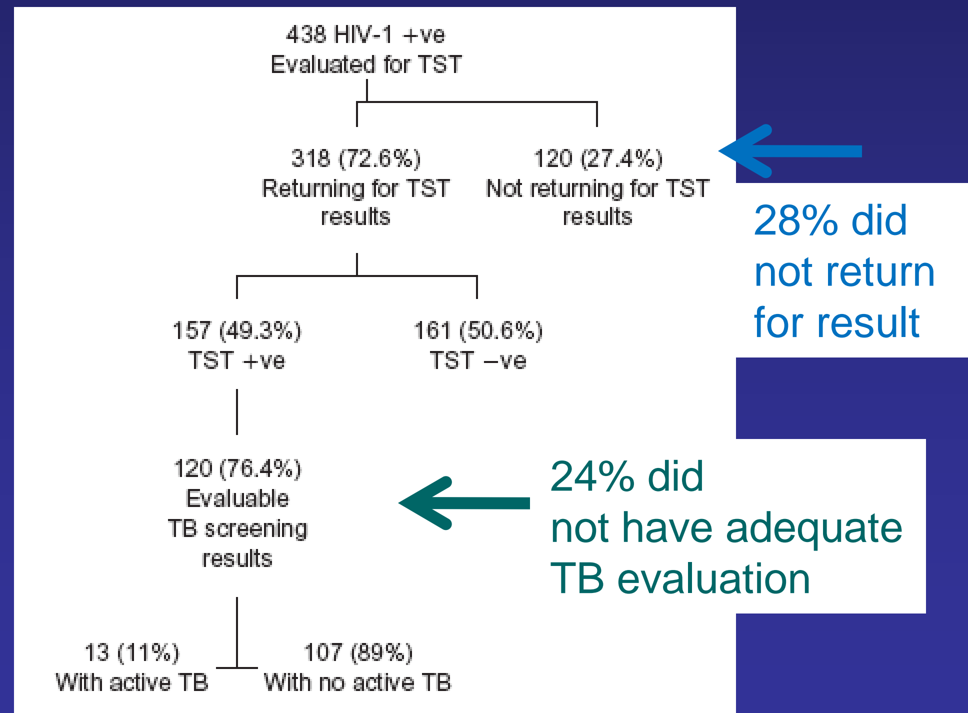
- Studies from South Africa have found a 2% prevalence among HIV-infected pregnant women screened in antepartum by symptom screen *(Kali JAIDS 2006)*
- 11% prevalence among tuberculin skin test (TST) positive South African HIV+ women assessed during post-natal follow-up *(Nachega AIDS 2003)*
- 1.4% prevalence 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 preformed 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.



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)

	Total population, %; Patients with advanced HIV disease,[a] %					
Screening criteria	Sensitivity	Specificity	PPV	NPV	Positive LR	Negative LR
WHO symptoms[b] alone	54.5; 54.5	90.9; 88.8	7.7; 17.6	99.3; 97.8	6.0; 4.9	4.9; 0.5
WHO symptoms or expanded criteria[c]	63.6; 63.6	89.7; 87.6	8.0; 18.4	99.4; 98.2	6.2; 5.1	0.4; 0.4
WHO symptoms or TST positivity[d,e]	100; 100	71.0; 70.0	4.7; 12.9	100; 100	3.4; 3.3	0.0; 0.0
WHO symptoms or abnormal chest radiograph	55.6; 55.6	73.0; 67.5	9.4; 16.1	97.0; 93.1	2.1; 1.7	0.6; 0.7
WHO symptoms or TB-compatible chest radiograph[f]	50.0; 50.0	64.6; 67.4	5.8; 13.9	96.7; 92.8	1.4; 1.5	0.8; 0.7
WHO symptoms, expanded criteria, or abnormal chest radiograph	66.7; 66.7	69.7; 63.8	10.0; 17.1	97.6; 94.4	2.2; 1.8	0.5; 0.5
WHO symptoms, expanded criteria, or TB-compatible chest radiograph	55.6; 55.6	79.8; 76.3	12.2; 20.8	97.3; 93.8	2.7; 2.3	0.6; 0.6

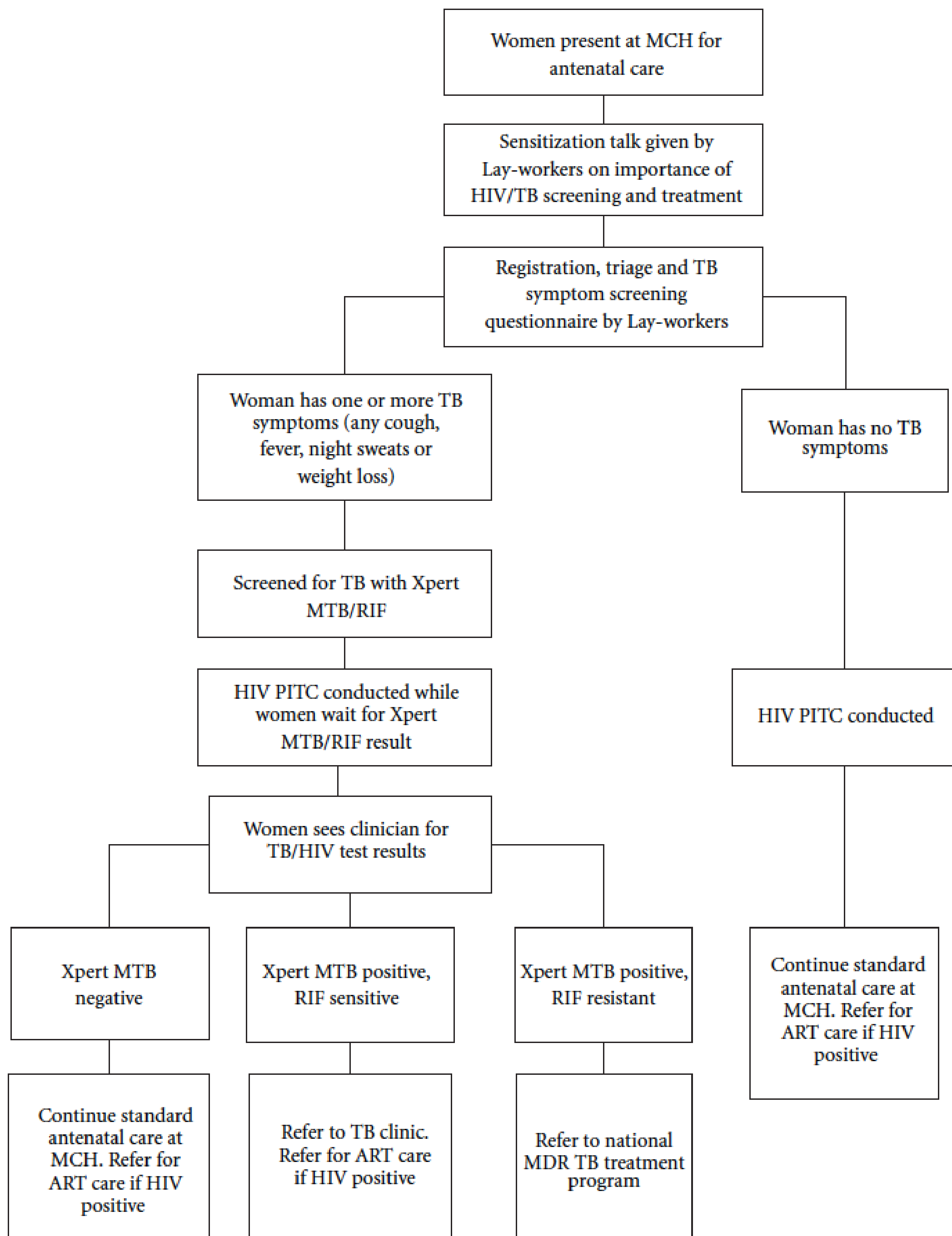
NPV of new WHO recommended symptom screen (cough, fever, weight loss) alone NPV 99.3% (97.8% if CD4<350)

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

TST

Pros

-Inexpensive, low tech

-Been standard for decades

Cons

-Requires return visit

-Operator dependent (placement and reading)

-Cross reactivity/false positive

IGRAs

Pros

-No return visit (result in 24 hrs)

-No cross reactivity with BCG

-No booster effect

-More likely positive in those recent MTB infection

Cons

-Fresh blood sample needed

-Expensive, needs a lab

-Cutoffs and interpretation

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

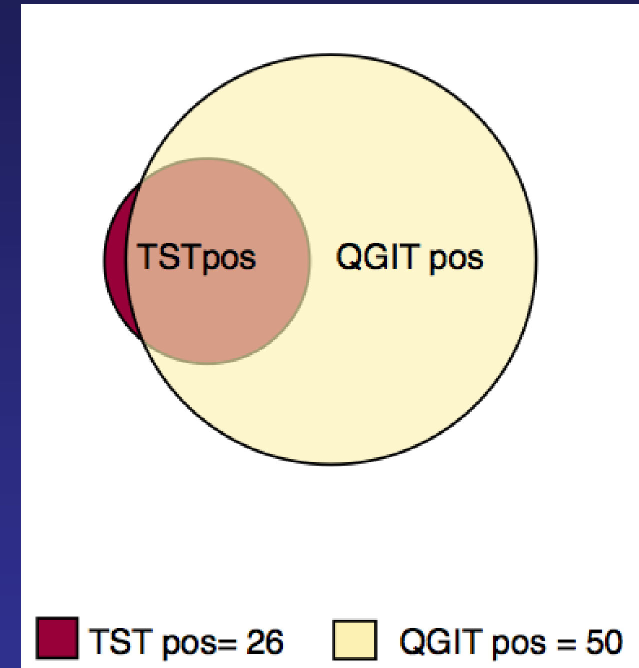
US data (Cohan, ACOG 2010 abstract)

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[1]

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

	Reduction in TB incidence	Study type	references
IPT	33% overall 62% if TST+	12 trials	Akolo Cochrane meta-analysis
HAART	60-80%	4 observational studies	Badri Lancet 2002 Santoro Lopes CID 2002 Golub AIDS 2009
HAART +IPT (not concurrent)	76-89%	2 observational Cohort	Golub AIDS 2007; AIDS 2009
HAART+IPT	50%	BOTUSA trial	Zamandari Lancet 2011
HAART +IPT concurrent		Ongoing trial	

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 pharmocokinetic 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

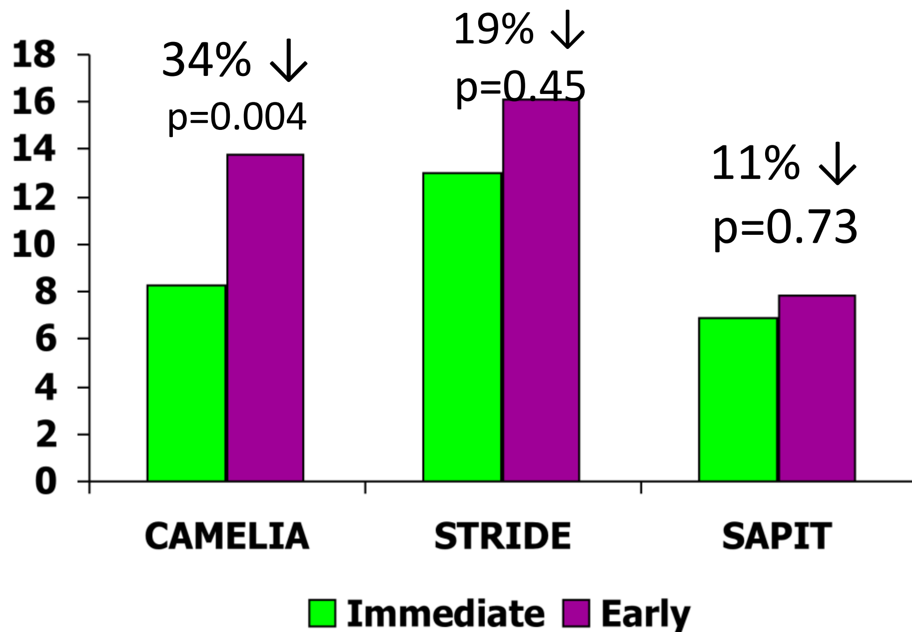
Key characteristics of trials of timing of ART during TB treatment

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

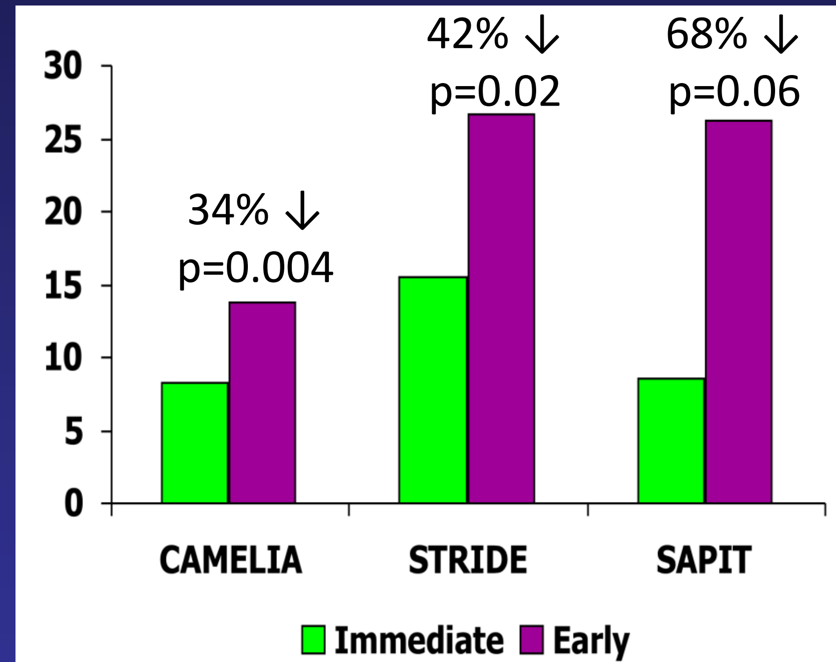
AIDS 2010 abstract THLBB106, CROI 2011 abstract 38, CROI 2011 abstract 39LB
October 22 NEJM 2011

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

Overall



CD4 < 50 in STRIDE and SAPIT



AIDS 2010 abstract THLBB106, CROI 2011 abstract 38, CROI 2011 abstract 39LB

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 maraviroc 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 1st 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

Drug	FDA	Crosses placenta	Breast-feeding	Issues in HIV pregnant women
INH	C	Yes	Yes	Hepatotoxicity esp Hep B, NVP
RIF	C	Yes	Yes	Drug interactions with NVP, PIs
rifabutin	B	Unk	unk	Drug interactions with PIs
EMB	B	Yes	Yes	
PZA	C	Yes	Yes	

Brost Obstet Gyn Clin 1997;Bothamley Drug Safety 2001;Shin CID 2003; Micromedex

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

Second line drugs for TB

Drug	FDA	Crosses placenta	Breast-feeding	Issues in HIV pregnant women
Strepto mycin/ AGs	D	Yes	Likely Yes	ototoxicity
Capreomycin	C	unk	No data	
FQs				
Cipro	C	Yes	AAP Yes WHO No	
Moxi	C	unk	unk	
Cycloserine	C	yes	unk	

Italics: case reports of use in pregnancy

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

Other drugs

Drug	FDA	Crosses placenta	Breast-feeding	Issues in HIV pregnant women
TMC 207	?	unk	unk	No data
Rifapentine	C	unk	unk	Teratogenic in rats/rabbits No data
Ethionamide	C	unk	unk	
Amoxicillin-clavulanate	B unk	Yes unk	Yes	

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

MDR TB in pregnancy

	N	Age	Prior TB	Resistance	Maternal	Rx	Infant
Nitta 1999 US	3		All	≥4	1 abort 2 FT		1 TST+
Lossneau 2003 US	1	22	No	4	PT	cured	Child sep x2 yrs
Shin 2003 US	7	21	All (4yrs)	≥4	7 FT	6 cured 1 failed	Healthy av.2.7 yrs
Tabrisi 2007 Afghan	1	18	Yes (2 yrs)	4	FT	Cured	Proph Healthy
Khan 2007 S. Africa	5 (3 HIV)	26	80% (7-15mo)	≥4	1 abort 3 FT,1PT All cx+ at delivery	1 failed 1 lost 1 default 2 treated	2/4 growth restricted 2/4 suspect TB
Palacios 2009 Peru	31 (3 HIV)	24.4	90%		5 SAB 1 SB 5 LB	61% cure, 13% died, 13% def	3 LBW,1PT 1 FDS,1 TB

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

BJ Medical College Sassoon Hospital Ward