

# Managing two infections – a review of the treatment of HIV-related tuberculosis

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*This presentation is intended for educational use only, and does not in any way constitute medical consultation or advice related to any specific patient.*

# Objectives

- Gain an understanding of the epidemiology of HIV-associated Tuberculosis (TB) globally
- Become familiar with the spectrum of TB infection/disease among HIV-positive persons
- Be able to discuss specific treatment considerations for TB disease in HIV-positive individuals



# 1.7 MILLION TB DEATHS

INCLUDING 0.4 MILLION TB DEATHS AMONG PEOPLE WITH HIV\*

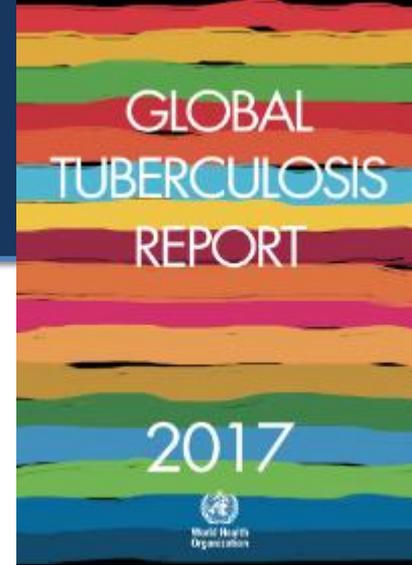
**TB is the top infectious killer worldwide**

TB is also the leading cause of deaths due to antimicrobial resistance and among people with HIV



**MDR-TB crisis with gaps in detection and treatment**

Only 1 in 5 needing MDR-TB treatment were enrolled on it



**US\$ 2.3 BILLION GAP**

**Funding shortfall for TB implementation**

- 10.4 million people with TB in 2016
- 600,000 with DR-TB



# Global TB/HIV report

## ACHIEVEMENTS IN 2016



**6.2 million lives saved of people with HIV** through scale-up of collaborative TB/HIV activities since 2005



**82% known HIV status** among notified TB cases in the Africa, up from 22% in 2006



**85% ART coverage** among notified TB cases living with HIV, up from 46% in 2006



**>1.3 million PLHIV started TB preventive Treatment** up from 27,000 in 2006



## KEY CHALLENGES



**37% of deaths among people with HIV due to TB**

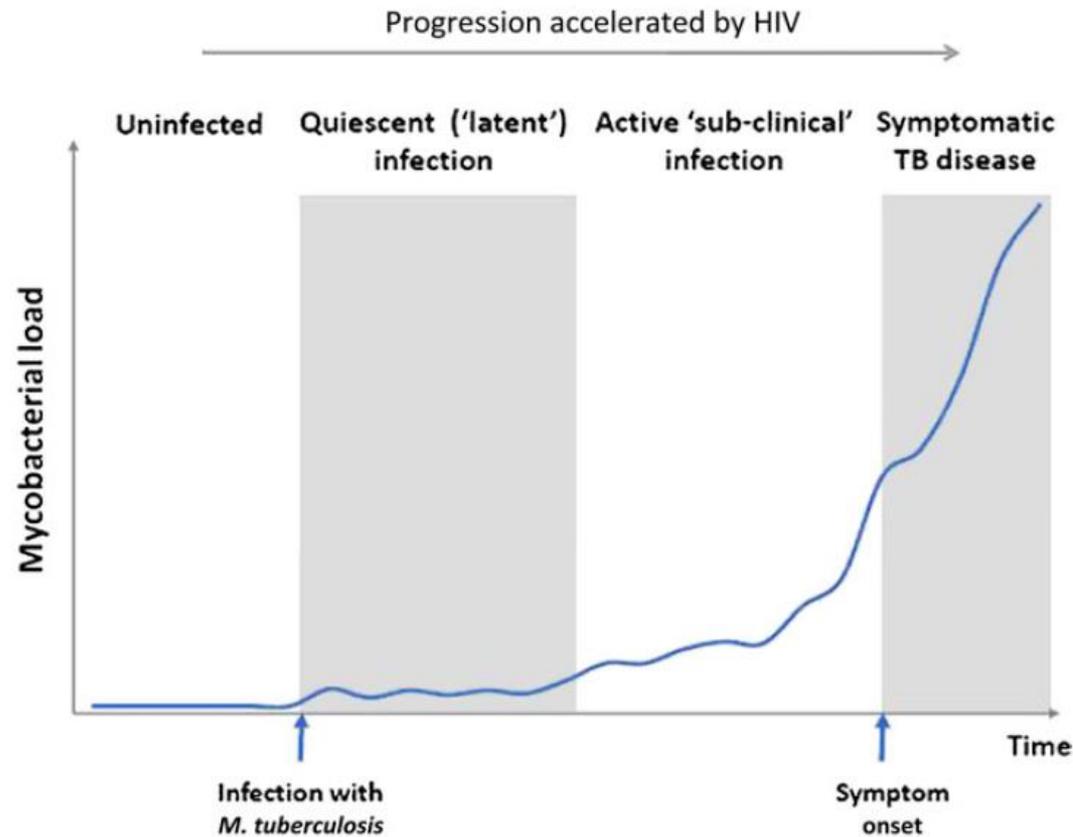
**54%**

**of all people with HIV-associated TB did not reach care** according to reported data



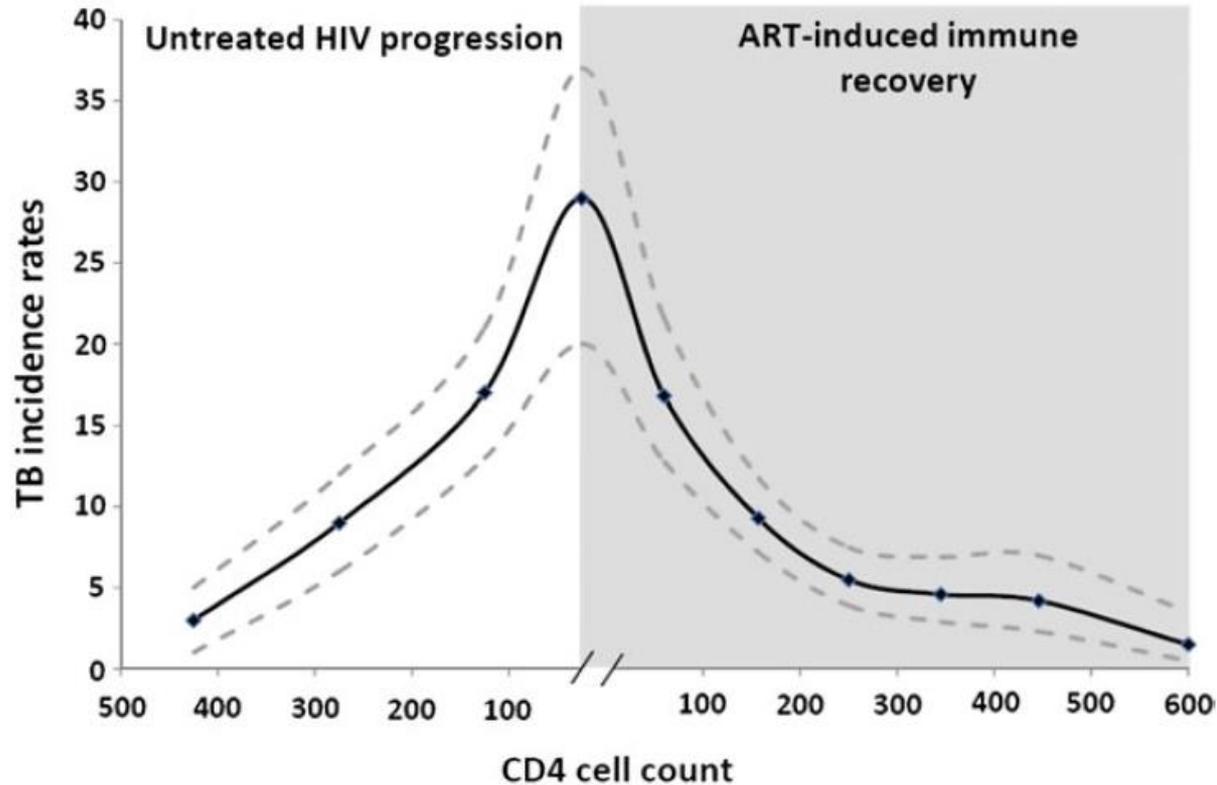
**18/30 countries with high burden of HIV-associated TB did not report IPT** for PLHIV newly enrolled in HIV care

# The Spectrum of TB Infection in Patients with TB and HIV



# Rates of TB disease depend on incidence in community of origin and underlying immunosuppression

Cases per 100/person-years



# Diagnostic testing for *M. tuberculosis* Infection

- Tuberculin skin test sensitivity <75%
  - $\geq 5$  mm is considered positive
  - If negative, repeat testing when  $CD4 > 200$  cells/ $\mu$ L; considered positive if previously  $\leq 4$ mm and now  $\geq 5$ mm
- IGRA sensitivity 69-89%
  - greater specificity in BCG-vaccinated individuals
  - If negative repeat testing when  $CD4 > 200$  cells/ $\mu$ L

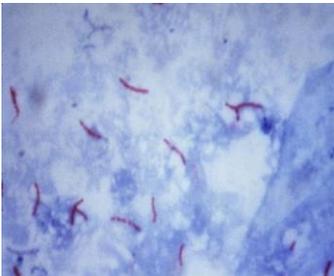
Huo Z and Peng L. BMC ID 2016  
Cobelens FG et al. CID 2006

## EVALUATING FOR TB DISEASE



# Diagnostic testing for *M. tuberculosis* Disease

- CXR—insensitive, may have normal findings in up to 1/3
- (AFB) sputum smear
  - Up to 70% may be AFB smear negative at presentation
- AFB sputum culture—gold standard, limit of detection 10 organisms/mL sputum

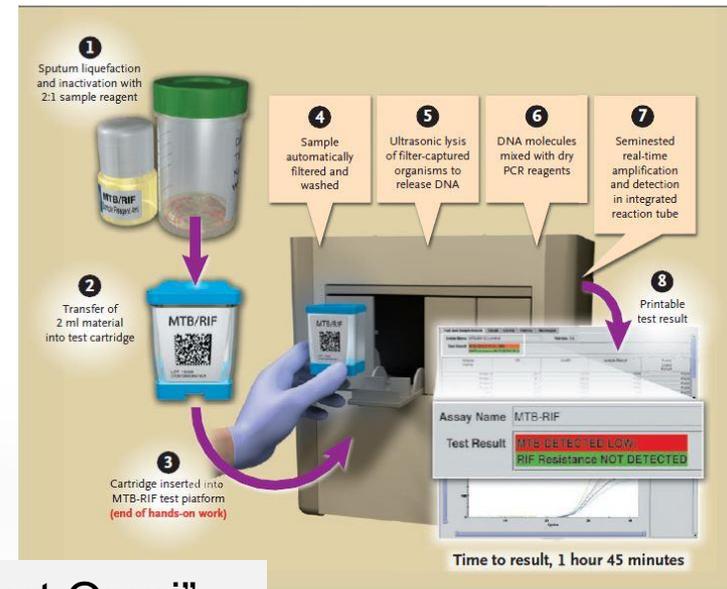


# Finding TB earlier to limit transmission, decrease time to effective treatment: Nucleic Acid Amplification Tests

## Molecular beacon (Xpert MTB/RIF)

- Identifies *M. tuberculosis* and detects mutations that confer resistance to rifampin
- Up to 67% of AFB *smear-negative* cases identified
- Newer generation (“Xpert-Ultra”) may approach sensitivity of culture

9 in.



“Xpert Omni”  
model is  
battery  
powered,  
wireless,  
internet  
connectivity

Boehme, C et al. N Engl J Med  
2010;363:1005-15.  
Alland D et al. CROI 2015, abstract # 9

# Finding TB earlier to limit transmission, decrease time to effective treatment: Nucleic Acid Amplification Tests

- **Amplified Mycobacterium Tuberculosis Direct Test**
  - HIV-positive individuals: sensitivity of 87.5% compared to culture, 70% in smear-negative (n=33 positive by solid culture media, 16/33 smear-positive)
- **Line probe assay (Hain)**
  - Tests for resistance to isoniazid and rifampin
  - Not widely available in the US
  - Likely as sensitive as Xpert

Alland D et al. CROI 2015, abstract # 91  
Schumacher SG, et al CROI 2017, abstract #76 LB  
Theron G, et al., Am J Respir Crit Care Med, 2011.  
Yoon C, et al., PLoS One 2012  
Santin M, et al., PLoS 2012  
Barreto et al. J Bras Pneumol 2014

# Other Diagnostic tests for *M. tuberculosis*

- AFB blood cultures
  - Common bloodstream infection in HIV-positive patients living in hyperendemic TB burden settings
- Urine culture for AFB
  - Yield up to 77%
- Urine-Lipoarabinomannan (LAM)
  - Tests for glycolipid in the cell wall of *M.tuberculosis*
  - Sensitivity higher in individuals with CD4 <50

Arthur, G., et al., Clin Infect Dis, 2001. 33(2): p. 248-56  
Varma, J.K., et al., Emerg Infect Dis, 2010. 16(10): p. 1569-75  
Theron G, et al., Am J Respir Crit Care Med, 2011. 184: 132-140.  
Yoon C, et al., PLoS One 2012  
Santin M, et al., PLoS 2012;7(3):e32482  
Lawn SD, et al. AIDS (London, England) 2012;26:1635-43.

# TB diagnostics for HIV-positive individuals: summary

- The best test is still culture: unacceptable diagnostic delays
- Universal offering of culture not feasible in many countries
- Point of care testing is improving but there are still gaps...
- What to do?
  - Maintain high index of suspicion
  - Empiric treatment followed by assessing clinical response
    - Pending culture results where available

# Patient with HIV/TB: HPI

20 y/o woman with newly diagnosed HIV who was admitted with cough, and lymphadenopathy.

Sputum – smear negative X 3

Gene Xpert MTB/RIF negative

IGRA positive

CD4 count 500 cells/ $\mu$ L

Lived in Uganda for most of her life prior to moving to the US



# Question #1

*What is your next step?*

- A. Cervical lymph node excisional biopsy
- B. Isoniazid/rifampin/pyrazinamide/ethambutol
- C. Bronchoscopy

# HPI

- Excisional cervical lymph node biopsy performed
  - Caseating granulomas throughout
  - Rare AFB
- Started on isoniazid, rifampin, ethambutol, pyrazinamide two weeks after initial presentation
- Sputum cultures grew *M. tuberculosis* after 13 days



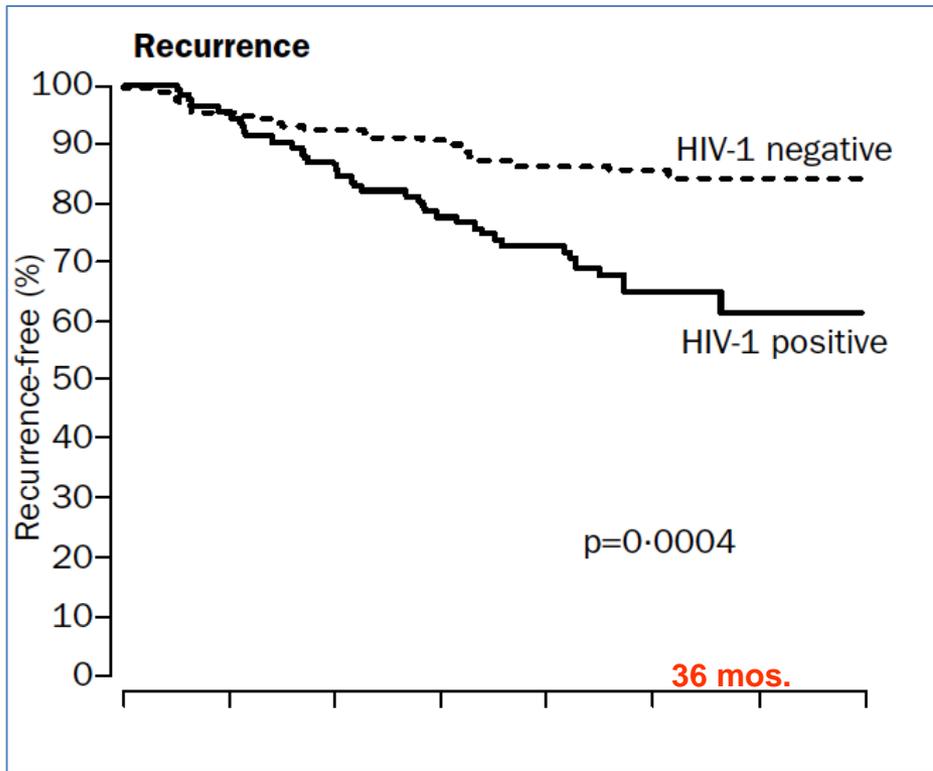
# Question #2

Initial isolate – drug-susceptible *M. tuberculosis*

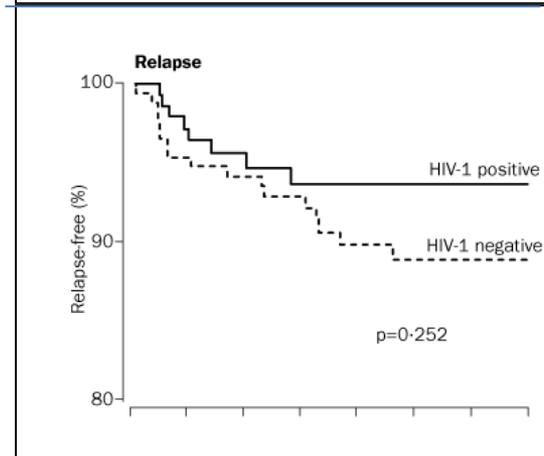
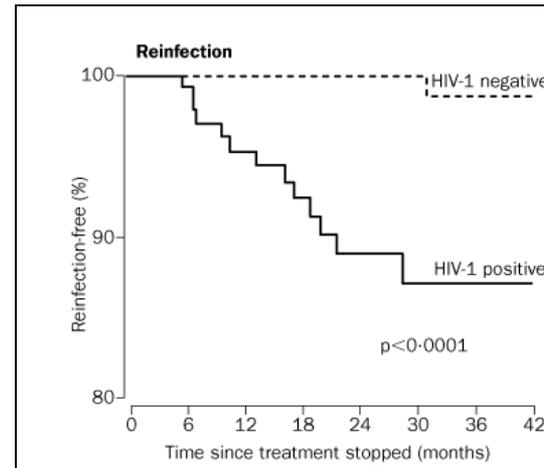
Patient does well clinically, and her 2-month sputum culture is negative. How long should she be treated for TB?

- A. 6 months
- B. 9 months
- C. 6 months followed by 6 additional months of INH

# TB recurrences most likely due to reinfection in higher burden settings in patients not on ART



Lancet 2001;358:1687-93



# (TB-HAART): prospective, international, randomized, placebo-controlled trial: 6 months of treatment associated with low relapse rates

- N=1675 patients, analyzed 1538; followed for 12 months, early vs. delayed ART, CD4 >350
- Primary endpoint: composite of death, failure of TB treatment, and recurrence at 12 months
- Proportion of recurrences **did not differ** significantly by group:
  - 19 (**2.6%** in early ART compared to 11 (**1.5%**) in delayed ART (RR 1.7, 95% CI 0.8–3.6; p=0.15).
- When stratified by CD4 cells count, treatment failure and recurrence **did not** differ significantly between groups
  - 28 (**4.3%**) of 647 in the early ART group compared with 39 (**5.8%**) of 675 in the delayed ART group (RR 0.74, 95% CI 0.47–1.20; p=0.23).

Mfinanga S, et al. Lancet Inf Dis 2014; 14: 563-71

# Summary of the Evidence: IDSA/ATS TB treatment Guidelines

- Standard 6-month regimens for most patients with drug-susceptible pulmonary TB
- Extend therapy to 9 months:
  - positive cultures at 2 months and cavitary disease
  - ART is not administered or CD4 <100
  - Other considerations for extending therapy: cavitary disease, diabetes, other immunocompromised state
  - WHO guidelines: no recommendations to extend treatment for drug-susceptible pulmonary TB

# Question #3

Daily directly observed therapy may be inconvenient for the patient and expensive for the TB Program. Is it safe and effective to use intermittent TB therapy?

- A. No – daily therapy should be used for the entire TB treatment course
- B. Yes, thrice-weekly is fine after the first 2 months
- C. Yes, thrice-weekly therapy is fine after 2 weeks

# Daily vs Intermittent Antituberculosis Therapy for Pulmonary Tuberculosis in Patients With HIV

## A Randomized Clinical Trial

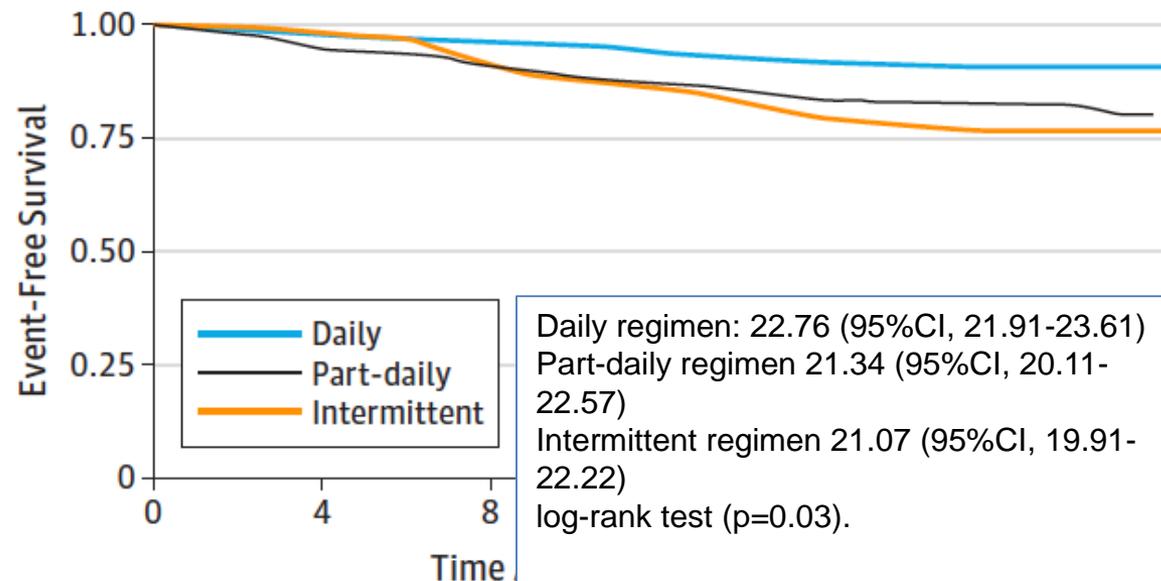
*JAMA Intern Med.* doi:10.1001/jamainternmed.2018.0141  
Published online March 5, 2018.

RCT, N=331 patients  
Primary outcome:  
proportion with a  
favorable response,  
defined as treatment  
completion with negative  
sputum cultures in the  
last 2 months of  
treatment

Outcome:  
Daily: 91%  
Fully Intermittent 77%  
P=0.006

Acquired rifamycin  
resistance only in  
intermittent therapy arms

Figure 2. Mean Survival Estimates for Time to an Unfavorable Event Among Antituberculosis Therapy Regimens



# Summary of the Evidence: IDSA/ATS TB treatment Guidelines

- Twice weekly therapy with rifabutin (RBT) and PI-based ART:
  - Associated with higher rates of relapse and the emergence of rifamycin resistance
  - Resistance more common in those with baseline CD4 counts <100 cells/ $\mu$ L
- Thrice-weekly RIF-based regimens during the intensive and continuation phase:
  - Higher rates of relapse and emergence of rifamycin resistance in HIV-positive individuals
  - **Higher risk of death**

Nahid P, et al. Clin Infect Dis 2016; 63 (7): e147-e195.  
Burman, B, et al. Am J Respir Crit Care Med. 2006; 176:350–6  
Narendran G, et al. Clin Infect Dis. 2014; 59:1798–804.  
Gopalan JAMA Int Med., 3/5/2018

# HPI continued

- She returns to clinic in 2 weeks feeling well.
  - When should we offer antiretroviral therapy?
  - What options are available for antiretroviral therapy?
  - What is the role for trimethoprim-sulfamethoxazole (TMP-SMX or co-trimoxazole) and when should this be offered?



# Trimethoprim-sulfamethoxazole/co-trimoxazole therapy for HIV-TB co-infected individuals

Study	Year	Study Design	Country	number	Mortality reduction
Wiktor et al.	1999	randomized controlled trial	Cote D'Ivoire	771	46%
Zachariah et al	2003	cohort study	Malawi	1,986	19%
Mwaungulu et al.	2004	cohort study	Malawi	717	22%
Grimwalde	2005	cohort study	South Africa	3,325	29%
Nunn	2008	randomized controlled trial	Zambia	1,003	21%

# Trimethoprim-sulfamethoxazole (co-trimoxazole) therapy for patients with TB and HIV

- US guidelines: initiate when CD4 count is less than 200 cells/ $\mu$ L, stop when the CD4 count  $>200$  for 3 months
- WHO guidelines: initiate irrespective of CD4 count, continue while on TB treatment
  - Discontinue after TB treatment if:
    - clinically stable on ART, with evidence of immune recovery and viral suppression
  - However, continue if malaria and severe bacterial infections are highly prevalent, irrespective of CD4 count

# Question #4

Should this patient be started on antiretroviral therapy (ART) during TB treatment, and if so, when?

- A. No – wait until TB treatment has been completed
- B. Yes, start ART after 2 months of TB treatment
- C. Yes, start ART after 2 weeks of TB treatment

# Trials of timing of ART during TB treatment

Study	Setting	Key enrollment criteria	Median CD4 (IQR)	Primary endpoint	Outcome
CAMELIA NEJM 2011	Cambodia, n=661	Smear +, CD4 < 200	25 (10 - 56)	Death	Decreased mortality (34%, p=0.004)
STRIDE NEJM 2011	Multi-national, n=809	Clinical TB, CD4 < 250	77 (36 – 145)	AIDS or death	Decreased mortality if CD4<50-42% ↓ p=0.02) (overall relative decrease: 19%, p=0.45)
SAPiT NEJM 2010, 2011	South Africa, n=642	Smear +, CD4 < 500	150 (77 – 254)	AIDS or death	Mortality if CD4<50 68% ↓ p=0.06 (overall relative decrease 11% in early group, p=0.73)
TB-HAART Lancet ID, 2014	Multi-national, operational conditions, n=1675	Smear + CD4 >220	367 (289- 456)	composite endpoint: relapse, treatment failure or death	No difference: early ART 3.0% mortality, late ART 2.0% mortality

N Engl J Med. 2011 Oct 20;365(16):1471 – 501  
Mfinanga S, et al. Lancet Inf Dis 2014; 14: 563-71

# Timing of ART in patients with TB

- Advanced AIDS (CD4 < 50): immediate ART (within 2 weeks) improves survival
  - Markedly increased risk of IRIS, including fatal IRIS events
  - Overall survival benefit despite IRIS
- CD4 > 50: early ART (~ 2 months) provides good balance of competing risks of death/AIDS vs. IRIS
- Caveats
  - CNS involvement – no benefit to immediate therapy, and there may be increased risk

# Adverse events during treatment of HIV-TB

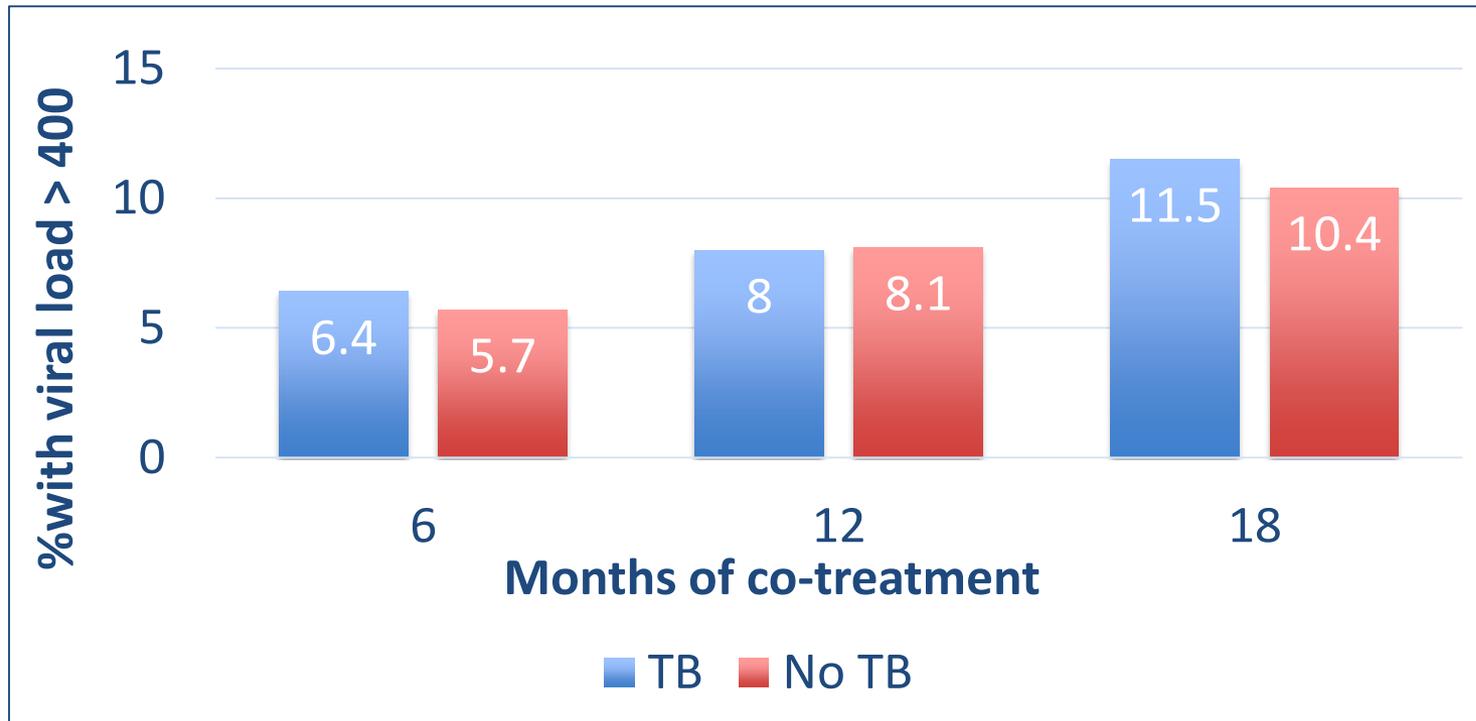
- 54% (99/167) had adverse events
- 34% interrupted TB or HIV therapy
- Common adverse events
  - GI intolerance
  - Skin rash (17%) - TB drugs (16), co-trimoxazole (7), nevirapine (2), other drugs (4)
  - hepatitis (6%) - TB drugs (6), unknown (5)

# Question #5

Our patient is doing well on standard 4-drug therapy. What antiretroviral therapy regimen would you recommend starting?

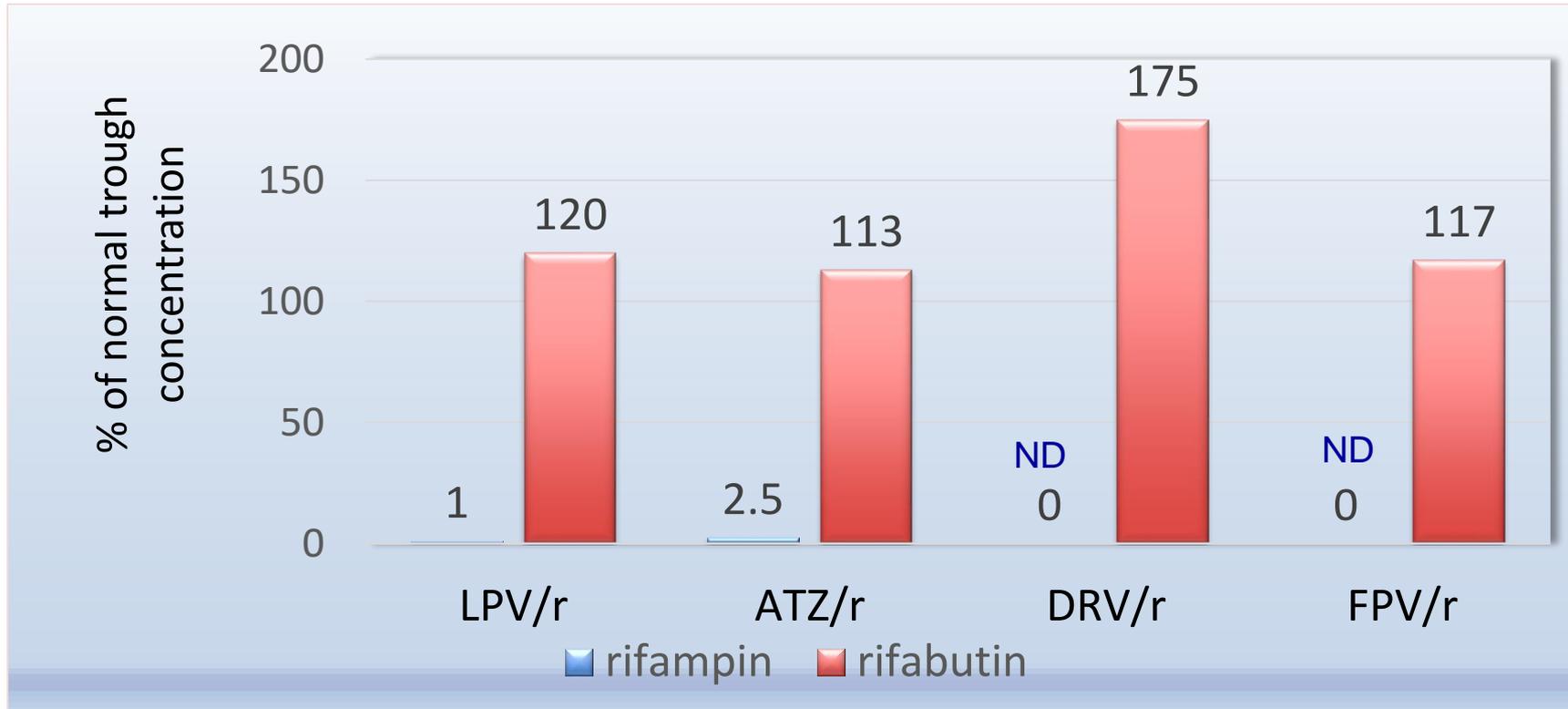
- A. Dolutegravir, tenofovir/emtricitabine (Truvada)
- B. Dolutegravir, tenofovir alafenamide/emtricitabine (Descovy)
- C. Efavirenz, tenofovir/emtricitabine (Atripla)
- D. Switch rifampin to rifabutin, and then start darunavir/ritonavir, tenofovir/emtricitabine (Truvada)

# Virological failure of efavirenz-based ART, among patients with and without TB



Modest reductions in EFV levels does not appear to reduce EFV activity  
Use of 800 mg dose of EFV – increased risk of neurological side effects

# Comparison of the effects of Rifampin vs. Rifabutin on trough concentrations of boosted protease inhibitors



AAC 2204;48:1553-60, AAC 2006; 50:3336-42, AAC 2010;54:4440-5, AAC 2008;52:534-8,

# Rifabutin (RBT) and TB therapy

- Rifabutin is likely as active as rifampin
- No dose adjustments of commonly-used protease inhibitors
- Decrease RBT from 300 mg daily to 150 mg daily when given with boosted PIs
- Caution – RBT dose would be inadequate if patient stopped PI
- No dose adjustment needed for dolutegravir and raltegravir

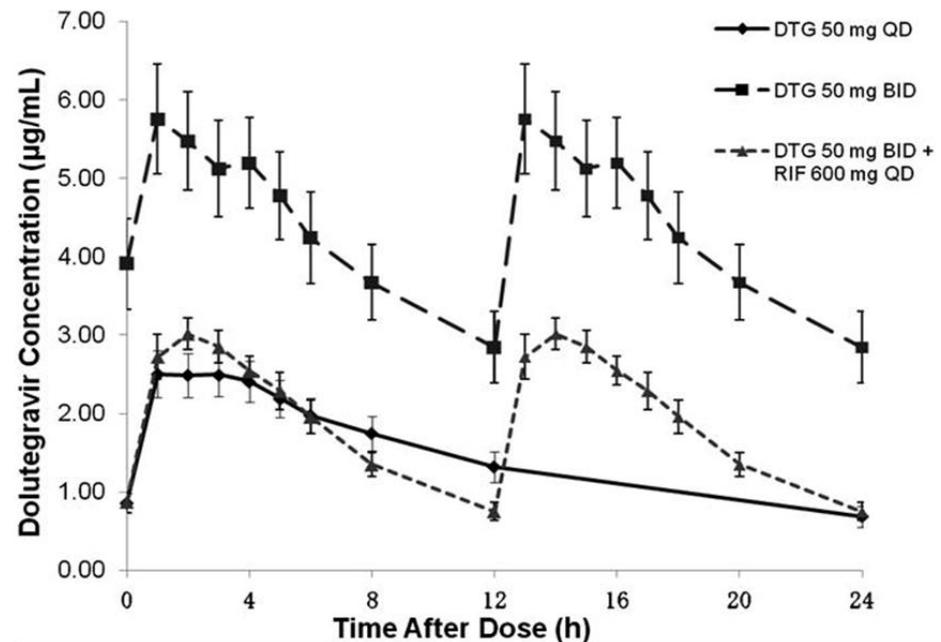
# Effect of rifampin on serum concentrations of dolutegravir (DTG) 50mg BID

- INSPIRING Phase 3b non-comparative open label RCT HIV-TB:

- DTG 50mg BID + 2NRTIs during TB tx and 2 weeks post therapy vs. Efavirenz (EFV) + 2NRTIs

- Week 24 of 52:

- 69 received DTG, 44 EFV
- Proportions with VL <50 c/mL:
  - DTG 56/69 (81%)
    - 5 discontinued due to protocol deviations/LTFU
  - EFV 39/44 (89%)
    - 2 discontinued due to adverse events



Dooley K et al. J Acquir Immune Defic Syndr 2013;62:21-7  
Dooley K et al. CROI #33,2018

# Rifampin Effect on Tenofovir Alafenamide (TAF) Plasma/Intracellular Pharmacokinetics

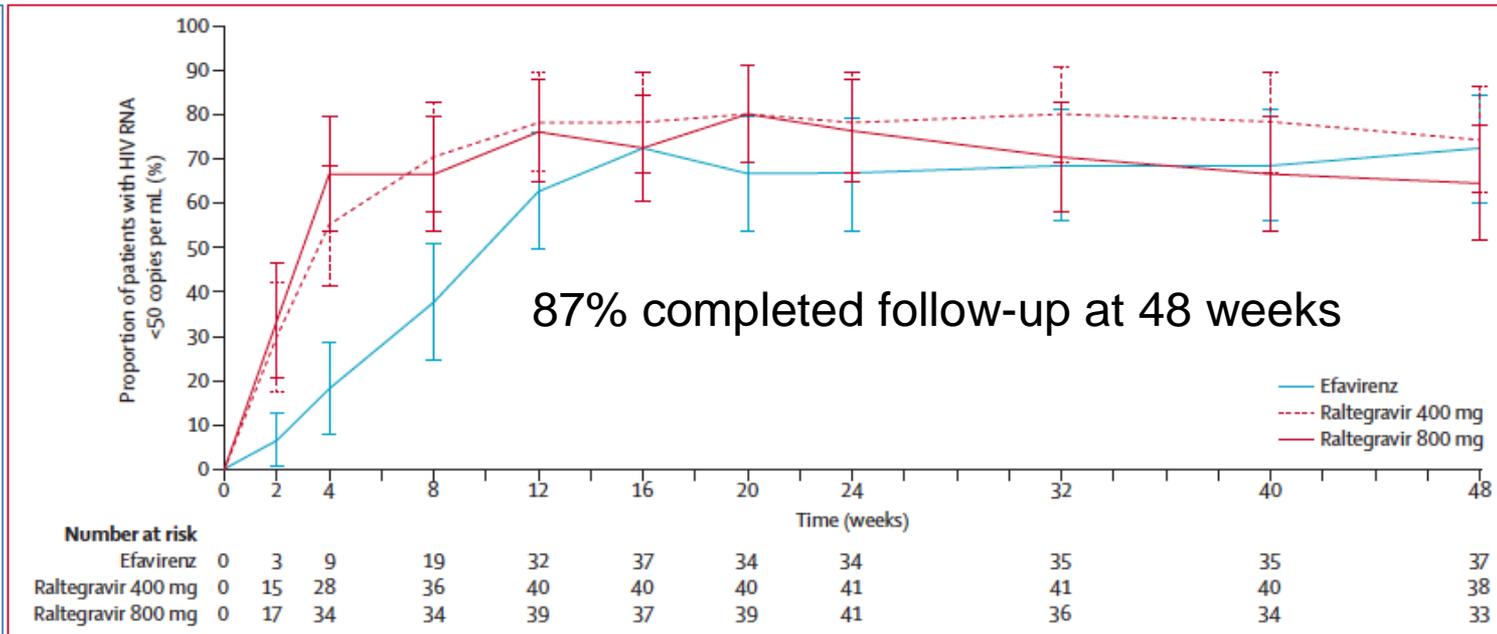
- Healthy volunteers between the ages of 18-65, n=17
- TAF/FTC once daily x 28 days with food, followed by TAF/FTC once daily with rifampin 600mg daily for 28 days followed by TDF 300mg daily x 38 days
- Intensive PK sampling on day 28, day 56 (TAF/FTC+ rifampin) and 84.
  - Measured TAF, TFV, FTC and (intracellular) IC TFV diphosphate
- Plasma TAF C<sub>max</sub> and AUC decreased by 45% and 47% respectively
- IC TFV-DP decreased by 40% *but still 82% higher than those achieved by standard dose of TDF*

# Rifampin and Raltegravir

- Raltegravir concentrations are decreased when co-administered with rifampin
  - Increasing the dose to 800mg BID mitigates this interaction
  - Unclear if this is necessary to achieve virological suppression: REFLATE TB, Lancet 2014:

N=155  
 51 in each arm  
**virological suppression at 24 weeks:**  
Raltegravir 400mg:  
 39 patients  
 (76%, 95% CI 65–88)

Efavirenz:  
 32 patients  
 (63%, 49–76)



Wenning LA, et al. Antimicrob Agents Chemother: 2009



# Recommended regimens for co-treatment of HIV-TB

- Efavirenz + 2 nucleosides (preferred)
  - Extensive experience among patients with HIV-TB
- Raltegravir (RAL) or dolutegravir (DTG) + 2 nucleosides
  - Recommendation is still to increase doses of Raltegravir to 800mg BID; likely 400mg BID is safe
  - Use increased doses of dolutegravir of 50mg BID
  - Do not use elvitegravir-containing regimens
- Rifabutin-based TB treatment
  - Alternative when PI class needed or would prefer not to double the dose of dolutegravir

# Types of immune reconstitution inflammatory syndrome (IRIS) events in HIV-TB

Fevers

New or worsening adenitis

New or worsening pulmonary infiltrates, including respiratory failure

New or worsening pleuritis, pericarditis, or ascites

Intracranial tuberculomas, worsening meningitis

Disseminated skin lesions

Epididymitis, hepatosplenomegaly, soft tissue abscesses

# Management of IRIS

- Anticipate IRIS events – discuss beforehand with patient and other care providers
- Rule out other possible causes – bacterial infections, a 2<sup>nd</sup> OI, inadequate Rx for OI, drug-resistant pathogen
- For relatively severe manifestations, prednisone is reasonable
  - 1 mg/kg (1.5 mg/kg with rifampin), tapering over 4-6 weeks

# Starting ART during TB treatment – summary of the steps required

Start TB therapy, manage side effects

Start TMP-SMX if indicated

Discuss initiating ART

Coordinate start of ART: (~ 2 weeks for CD4 < 50, ~ 2 months for CD4 > 50)

Use DOT visits to increase adherence to ART

Anticipate and manage IRIS

Provide psychosocial support and coaching

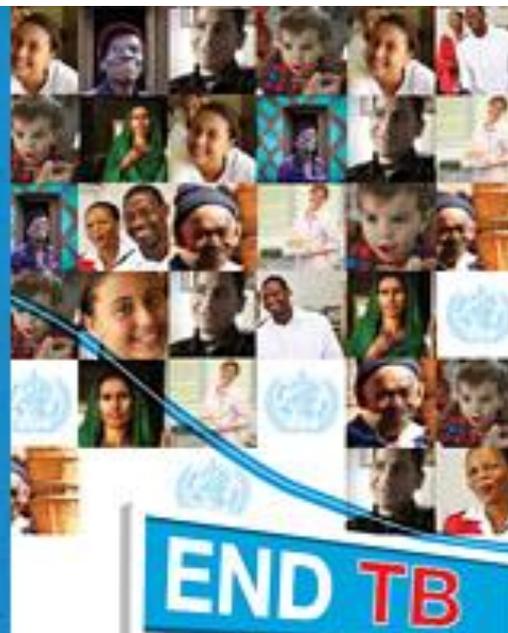
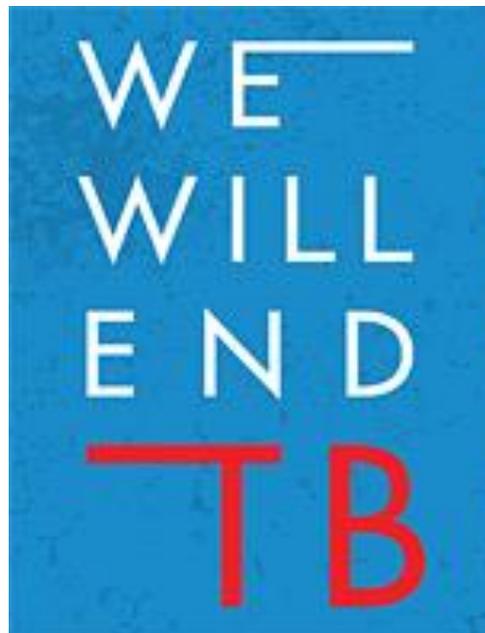
# Latent tuberculosis infection

Updated and consolidated guidelines for programmatic management

THE  
**END TB**  
STRATEGY



World Health Organization



# LTBI regimens

- INH daily for 9 months + B6 25mg daily
- Rifampin (RIF) given daily for 4 months
  - Substantial drug interactions, all medications should be reviewed
- INH-rifapentine once weekly for 12 doses
  - 2.6% HIV-infected—unclear if on ART in initial studies
  - Can now be given self-administered or as directly observed therapy
  - Likely safe if patients are on efavirenz or raltegravir based regimens

Podany, CROI abstract # 455, 2018  
Weiner M, J antimicrob Chemother 2014

# ONE MONTH OF RIFAPENTINE/ISONIAZID TO PREVENT TB IN PEOPLE WITH HIV: BRIEF-TB/A5279

- Phase 3 RCT, open-label, 10 countries participating, n=3,000
  - >13 years, living in high TB-burden areas OR who were TST/IGRA positive
  - ART with efavirenz or nevirapine; followed for 3 years
  - Randomized to 1HP\* or 9H\*
  - Primary endpoint: incidence rates of active TB, TB death or death from an unknown cause

- Results:
  - **634 (21%) had positive TST or IGRA**
  - Primary endpoint:
    - N=34 1HP arm; 35 9H arm, for incidence rates of 0.69/100 PY for 1HP and 0.72/100 PY for 9H (IR difference = -0.025, upper 95% CI: 0.31, Table).
    - TB incidence rates were higher among those with +TST/IGRA but not different between the two arms
  - Treatment completion was 97% with 1 HP vs. 90% in the 9H arm, p<0.01

# Summary – treatment of HIV-related TB: active TB treatment issues

- How long should active TB treatment be given?
  - 6 months for pulmonary disease (selected individuals may be offered 9 months)
- Daily DOT is a hassle – can intermittent therapy be used?
  - Intermittent therapy is no longer recommended, even three times per week

# Summary – treatment of HIV-related TB: issues with antiretroviral therapy

- Should antiretroviral therapy be used during active TB treatment?
  - Yes, for all patients
- What regimens can be used for co-treatment of HIV and TB?
  - Preferred: efavirenz-based ART + rifampin-based TB treatment
  - Integrase-inhibitor based ART (rifampin or rifabutin)
  - PI-based ART + rifabutin-based TB treatment
- When should ART be started?
  - 2 weeks to 2 months after starting active TB treatment

# Patient follow-up

- In addition to being newly diagnosed with TB and HIV, she was also 15 weeks pregnant
  - emtricitabine/tenofovir/efavirenz initiated after 2 weeks of tolerating TB treatment
  - TB treatment completed at 6 months



# Thank You!

