New Trials for Treating LTBI in HIV-infected Patients

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Conflict of interest disclosure

I have no conflicts of interest
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Outline

Latent *M. tuberculosis* Infection in HIV-Positive Persons

- Epidemiology
- Treatment
  - Regimens
    - 6-9 months of isoniazid
    - Short-course: 3-4 months of rifamycin-based therapy
    - Ultra short-course: 4-6 weeks of rifamycin-based therapy
  - Strategies
    - Antiretroviral therapy + isoniazid
    - Extended duration / continuous isoniazid
    - Repeated courses of short-course treatment
- Focus: recent trial results, and ongoing + planned trials

Prevalence of latent *M. tuberculosis* infection in the world

One-quarter of the global population is infected with *M. tuberculosis*

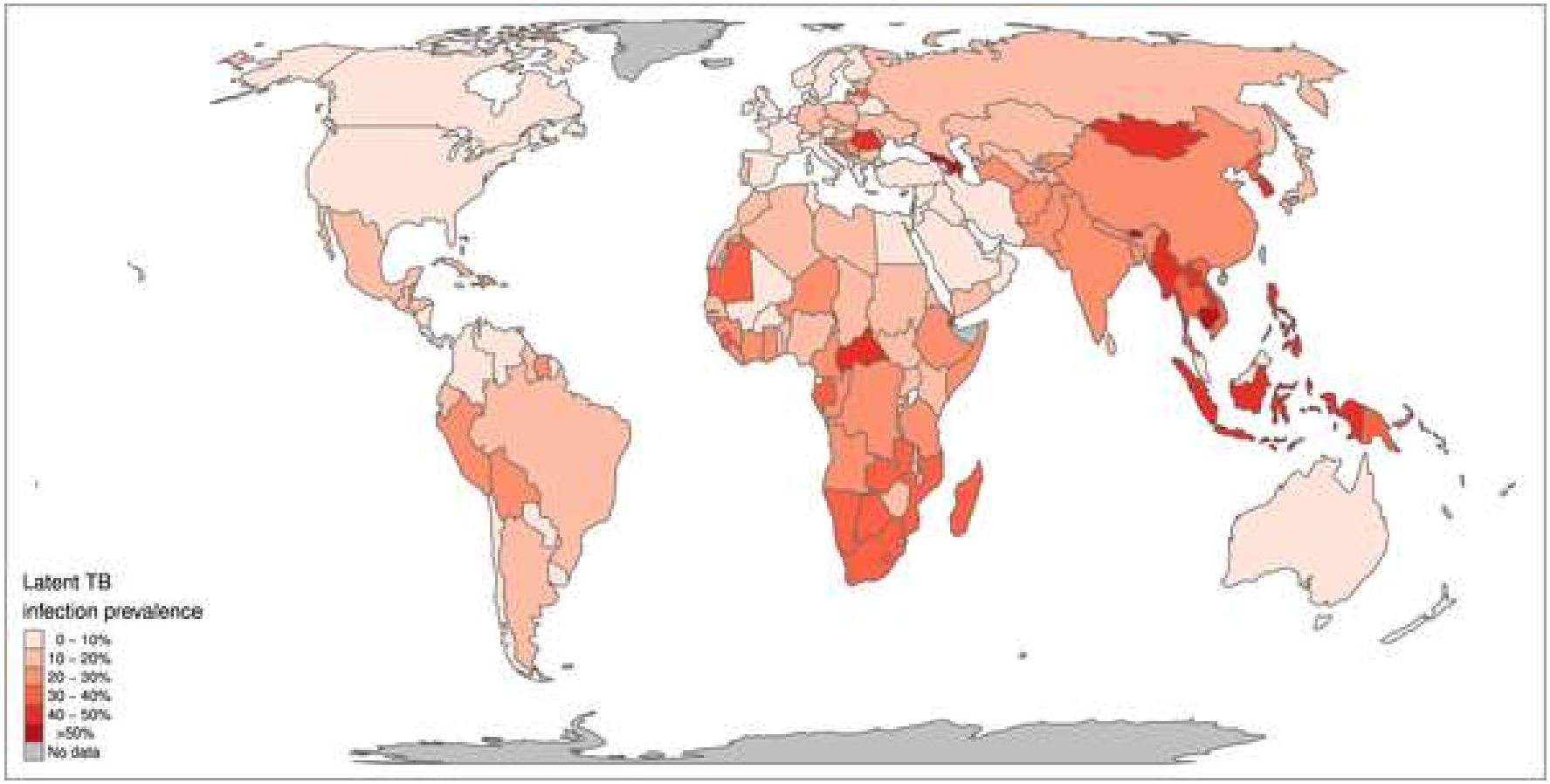
- Global population November 2018: 7.6 billion
- Approximately 2 billion people infected
  - Raviglione M. JAMA 1995;273:220. Dye C et al. JAMA 1999;282:677. Houben R PLoS Med 2016.
- Prevalence of *M. tuberculosis* infection varies by location
  - High TB incidence setting: (Kampala, Uganda): 49% (95% CI: 44-55)
    - Kizza FN. BMC Infect Dis 2015:165
  - Low TB incidence setting (United States): ~5%
    - Miramontes R. PLoS ONE 2015:10 (11):e0140881
    - Mancuso JD. Am J Respir Crit Care Med 2016 Feb 11.
    - Ghassemieh BJ. Am J Respir Crit Care Med 2016 Feb 18.

Approximately 10% of global TB cases are HIV-positive

- WHO Global TB Report. October 2018

Global map of prevalence of latent TB infection

From this reservoir of ~2 billion infected persons, 100-200 million TB cases could develop



Houben RMGJ, Dodd PJ (2016) The Global Burden of Latent Tuberculosis Infection: A Re-estimation Using Mathematical Modelling. PLOS Medicine 13(10): e1002152. https://doi.org/10.1371/journal.pmed.1002152
https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1002152

PLOS | MEDICINE

HIV is the strongest risk factor for progression from *M. tuberculosis* infection to TB disease

Risk Factor	Fold risk of progression to TB
HIV	50 - 110
Transplant immunosuppression	20 - 74
Silicosis	30
Malignancy (head and neck)	9 - 16
Recent infection (<2 yrs)	15
Renal failure—dialysis	10 - 25
Apical fibronodular changes on CXR	6 - 19
TNF-alpha inhibitors	2 - 9
Glucocorticoids	5
Age ≤ 4 years	2 - 5
Diabetes mellitus	2 - 4
Underweight	2 - 3
Smoking	2 - 3
Alcohol	2

Adapted from: Dheda K. Lancet 2016;387;1211. Cheng M CID 2017;64:635. Lee MR CID 2017;64:719

Treatment of *M. tuberculosis* Infection

Current Regimens

Regimen	Efficacy	Effectiveness	Comments
9 months INH daily	90%	25-88% (median:60%)	6 and 12 months well-studied; 30-60% completion
4 months rifampin daily	---	50-90% (estimated)	Limited data in HIV+ persons
3 months INH + rifampin daily	---	41-59%	An alternative; hepatoxicity
3 months INH + rifapentine once-weekly	90% (estimated)	90% (estimated)	≥82% completion Lower rates when self-administered than DOT

Treatment of *M. tuberculosis* infection

- 3-4 month rifamycin-based regimens are an alternative to 6-9 months of INH
  - WHO. Latent TB Infection. Updated and Consolidated Guidelines. 2018.
    - High and low TB incidence settings
      - 3 months of INH + rifampin (3HR)
      - 3 months of INH + rifapentine (3HP)
    - Low TB incidence settings
      - 4 months of rifampin (4R)
        - Concern re: undiagnosed active TB in HIV+ persons, particularly in high TB/HIV settings: treating active TB with rifampin alone, increasing the risk of acquired rifampin resistance
  - Given similar efficacy yet higher treatment completion rates with shorter regimens, the 3-4 month regimens could have higher effectiveness than 9INH

4 months of daily rifampin

- 4 months of daily rifampin vs 9 months of daily INH
- Open-label, non-inferiority study
  - Primary endpoint: confirmed active TB
    - Non-inferiority margin: 0.75%
- Australia, Benin, Brazil, Canada, Ghana, Guinea, Indonesia, Saudi Arabia, South Korea
- ≥18 years old, +TST or IGRA, increased TB risk
  - 98% TST+
  - 71% close contacts of confirmed TB cases
  - 4% (n=242) HIV+
- Follow-up: 28 months from enrollment

Menzies D. N Engl J Med 2018;379:440-453.

4 months of daily rifampin

Variable	9INH	4RIF	Rate Difference (95% CI)	P-value
Number of participants	3,416	3,443		
Completed 28 months of f/u	92%	92%		
Person-years of f/u	7,652	7,723		
Confirmed active TB cases	4	4		
TB case rate per 100 person-years	0.05 (0.02, 0.14)	0.05 (0.02, 0.14)	<0.01 (-0.14, 0.16)	0.76

Menzies D. N Engl J Med 2018;379:440-453.

4 months of daily rifampin

Variable	9INH	4RIF	Rate Difference (95% CI)	P-value
Number of participants	2,809	2,887		
Treatment completion	63%	79%	-15%	<0.001
Permanent drug discontinuation for grade 3, 4, 5 event due to study drug	59 (2.1%)	24 (0.8%)	-1.3 (-1.9, -0.6)	<0.001
Grade 3 or 4 hepatoxicity	49 (1.7%)	8 (0.3%)	-1.5 (-2.0, -0.9)	<0.001
Death	1 (<0.1%)	0	<0.1 (-0.1, 0.0)	0.31

Menzies D. N Engl J Med 2018;379:440-453.

4 months of daily rifampin

- Conclusions: 4RIF compared to 9INH:
  - As effective
  - Higher treatment completion rate
  - Safer
  - Also effective and safe in children
    - Diallo T. N Engl J Med 2018;379:454-463
  - Limitations
    - Low number of TB cases
    - Few HIV+ participants

Menzies D. N Engl J Med 2018;379:440-453.

3 months of weekly INH + rifapentine

Tolerability and Safety in HIV + Persons

- TBTC Study 26 / ACTG 5259 amended to enroll 191 additional HIV+ persons; 403 total. There were 399 for efficacy evaluation. Median CD4 ~500. Follow-up complete September 30, 2013

Characteristic	3HP N=207	9H N=186	P-value
Treatment completion (MITT)	183/206 (89%)	123/193 (64%)	<0.001
Discontinue— adverse drug reaction	7 (3%)	8 (4%)	0.79
Grade 3 toxicity	14 (7%)	18 (10%)	0.36
Grade 4 toxicity	4 (2%)	10 (5%)	0.10
Grade 5 (death)	6 (3%)	5 (3%)	1.00
Hepatotoxicity → drug discontinuation	2 (1%)	8 (4%)	0.05
Possible flu syndrome	2 (1%)	0 (0%)	0.50

3 months of weekly INH + rifapentine

Effectiveness in HIV+ Persons

Modified Intention to Treat Population. Non-inferiority margin: 0.75%

Treatment Arm	N	#TB Cases	TB per 100 p-y	Cumulative TB Rate (%)	Difference in Cumulative TB Rate	Upper bound of 95% CI (%)
9H	193	6	1.25	3.50	-2.49	0.60
3HP	206	2	0.39	1.01		

Sterling TR, Scott N et al. AIDS 2016;30:1607-15.

4 weeks of daily INH + rifapentine

Brief Rifapentine-INH Efficacy for TB Prevention (BRIEF-TB)
AIDS Clinical Trials Group 5279

- Population: HIV-positive persons ≥ 13 years old in high TB incidence settings
  - ≥ 60 / 100,000 population
- Intervention: daily INH + rifapentine for 1 month
- Comparator arm: daily INH for 9 months
- Antiretroviral therapy: efavirenz or nevirapine-based
- Follow-up: 3 years after last participant enrolled
- Primary endpoint: TB (confirmed or probable), TB death, death due to unknown cause
- Non-inferiority design:
  - Expected TB rate in 9H arm: 2.0 per 100 person-years
  - Non-inferiority margin: 1.25 per 100 person-years

Swindells S, Chaisson RE. CROI March 2018

4 weeks of daily INH + rifapentine

Brief Rifapentine-INH Efficacy for TB Prevention (BRIEF-TB)
AIDS Clinical Trials Group 5279

Characteristic	9H N=1504	1HP N=1496
Median age (years)	35	35
Male sex	692 (46%)	694 (46%)
Median BMI	23.5	23.6
Median CD4	469	473
ART at entry	749 (50%)	747 (49%)
TST-positive	21%	21%

Swindells S, Chaisson RE. CROI March 2018

4 weeks of daily INH + rifapentine

Brief Rifapentine-INH Efficacy for TB Prevention (BRIEF-TB)
AIDS Clinical Trials Group 5279

Endpoint	9H N=1504	1HP N=1496	IRR (95% CI)
Primary endpoint All-comers	33/4896 p-y 0.67 / 100 p-y	32/4926 p-y 0.65 / 100 p-y	0.023 (-0.30, 0.35)
Primary endpoint CD4 ≤ 250	1.275 / 100 p-y	1.931 / 100 p-y	-0.656 (-2.06, 0.75)
Active TB, confirmed	14	18	
Active TB, probable	10	11	
Death due to TB	2	0	
Death-unknown cause	7	3	

Swindells S, Chaisson RE. CROI March 2018

4 weeks of daily INH + rifapentine

Brief Rifapentine-INH Efficacy for TB Prevention (BRIEF-TB)
AIDS Clinical Trials Group 5279

Endpoint	9H N=1498	1HP N=1488
Grade ≥ 3 adverse event	274 (18%)	250 (17%)
Treatment completion (self-report)	90%	97%
Premature drug discontinuation	2%	1%

Swindells S, Chaisson RE. CROI March 2018

ASTERoiD

Assessment of the Safety, Tolerability and Effectiveness of Rifapentine given Daily for LTBI

Six weeks of daily rifapentine vs. a comparator arm of 12-16 week rifamycin-based treatment of latent *M. tuberculosis* infection: assessment of safety, tolerability and effectiveness

TB Epidemiologic Studies Consortium: Part D
British Medical Research Council
TB Trials Consortium: Study 37

Enrollment to start early 2019

INH + ART to prevent TB

Randomized, double-blind placebo-controlled trial

- **Khayelitsha, South Africa**
- **Randomly assigned 12 months of INH (n=662) vs. placebo (n=667) to persons on ART**
- **Primary endpoint: time to incident TB**

	INH	Placebo	HR	95% CI
TB per 100 p-y	**2.3**	**3.6**	**0.63**	**0.41,0.94**

- **The beneficial effect of INH was not limited to those who were TST+ or IGRA+**
- **Without a more predictive test, authors suggest that INH should be recommended to all patients receiving ART in moderate or high TB incidence areas, regardless of TST or IGRA status.**

Rangaka MZ. Lancet 2014;384:682-90.

ART with or without INH

Cote d'Ivoire

- **ART started according to WHO guidelines**
  - **With or without INH (6 months) started within 1 month**
- **ART started immediately**
  - **With or without INH (6 months) started within 1 month**
- **Factorial design; no interaction between INH, early ART**
- **Follow-up: 30 months**
- **2,056 patients; 41% with baseline CD4 ≥ 500**
- **Primary outcome: death, any AIDS event, non-AIDS invasive bacterial disease, non-AIDS malignancy (combined)**
- **35% were QuantiFERON positive**
- **Early ART and INH independently ↓ severe illness**

Intervention	Adjusted HR	95% CI	P-value
Early ART	0.56	0.41, 0.76	< 0.001
INH	0.65	0.48, 0.88	0.005

Danel C—TEMPRANO Trial. N Engl J Med 2015;373:808-822.

Enhanced antimicrobial prophylaxis

Uganda, Zimbabwe, Malawi, Kenya

HIV+, ≥ 5 years old, CD4 < 100, starting ART

- **Enhanced prophylaxis (n=906):**
  - Continuous trimethoprim-sulfa
  - ≥12 weeks of INH/B6
  - 12 weeks of fluconazole
  - 5 days of azithromycin
  - 1 dose of albendazole
- **Standard prophylaxis (n=899):**
  - Continuous trimethoprim-sulfa

Hakim J. N Engl J Med 2017;377:233-45.

Enhanced antimicrobial prophylaxis

Uganda, Zimbabwe, Malawi, Kenya

HIV+, ≥ 5 years old, CD4 < 100, starting ART

Endpoint	Enhanced N=906	Standard N=899	P-value
Death at 24 weeks (1° endpoint)	8.9%	12.2%	0.03
TB	7.1%	10.2%	0.02
Cryptococcal infection	1%	2.6%	0.01
Candidiasis	1.1%	2.6%	0.02
New hospitalization	17%	20.7%	0.03

Hakim J. N Engl J Med 2017;377:233-45.

Empiric TB therapy vs. isoniazid in HIV+ adults starting ART

REMEMBER study

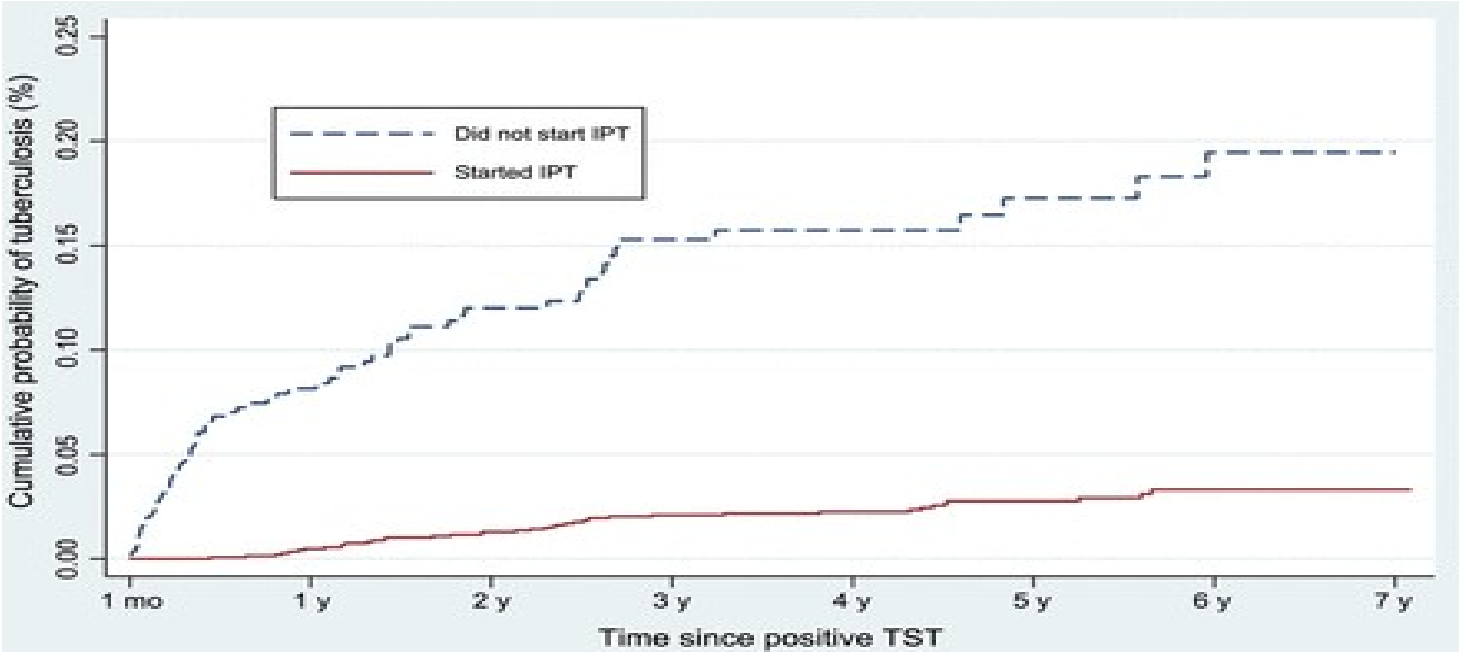
- **CD4 < 50**
- **Malawi, South Africa, Haiti, Kenya, Zambia, India, Brazil, Zimbabwe, Peru, Uganda**
- **Persons with confirmed or suspected TB excluded**
- **Primary endpoint: survival (death or unknown status) at 24 weeks**
  - **ART + anti-TB therapy (n = 424) 5% (3.5, 7.8)**
  - **ART + INH (n = 426) 5% (3.4, 7.8)**
- **Grade 3-4 lab abnormalities**
  - **ART + anti-TB therapy: 23%**
  - **ART + INH 23%**

Hosseinipour MC. Lancet 2016;387:1198-209.

Protective effect of INH through 7 years

Rio de Janeiro, Brazil

- **1,954 TST+/HIV+ persons**
  - **1,601 (82%) initiated INH**
    - **1,330 (83%) completed 6 months of INH**



Golub J. Clin Infect Dis 2015;60:639-45.

INH for 6 months vs. 36 months

in HIV+ persons

- Botswana
- Randomized double-blind placebo-controlled trial
- Tuberculin skin test-positive or -negative
- All patients received 6 months INH
  - INH vs. placebo for next 30 months
- Antiretroviral therapy provided if CD4 < 200
- INH dose: 300 mg + 25 mg B6

Samandari T. Lancet 2011;377:1588-98.

INH for 6 months vs. 36 months

	6H	36H	Hazard ratio	P-value
TB per 100 p-y (**All**)				
ITT (n=989 / 1,006)	1.26	0.72	0.57	0.047
PP (n=665 / 653)	1.18	0.51	0.43	0.045
TB per 100 p-y (**TST+**)				
ITT	2.22	0.57	0.26	0.019
PP	1.81	0.00	0.00	0.007

ITT: intention to treat **PP: per protocol**

Samandari T. Lancet 2011;377:1588-98.

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ITT	2.22	0.57	0.26	0.019
PP	1.81	0.00	0.00	0.007

TST-negative: HR = 0.75 P = 0.40

ITT: intention to treat **PP: per protocol**

Samandari T. Lancet 2011;377:1588-98.

TB Incidence after 36 months of INH
Botswana

- Post-trial observational analysis for durability of protection
  - 36 months vs. 6 months of INH

	Trial period	95% CI	Post-trial	95% CI
All participants	0.57	0.33, 0.99	0.82	0.46, 1.49
TST + participants	0.26	0.08, 0.80	0.40	0.15, 1.08

- In multivariable analysis, ART ↓ risk of death but not TB in post-trial period

Samandari T. AIDS 2015;29:351-9.

WHIP3TB

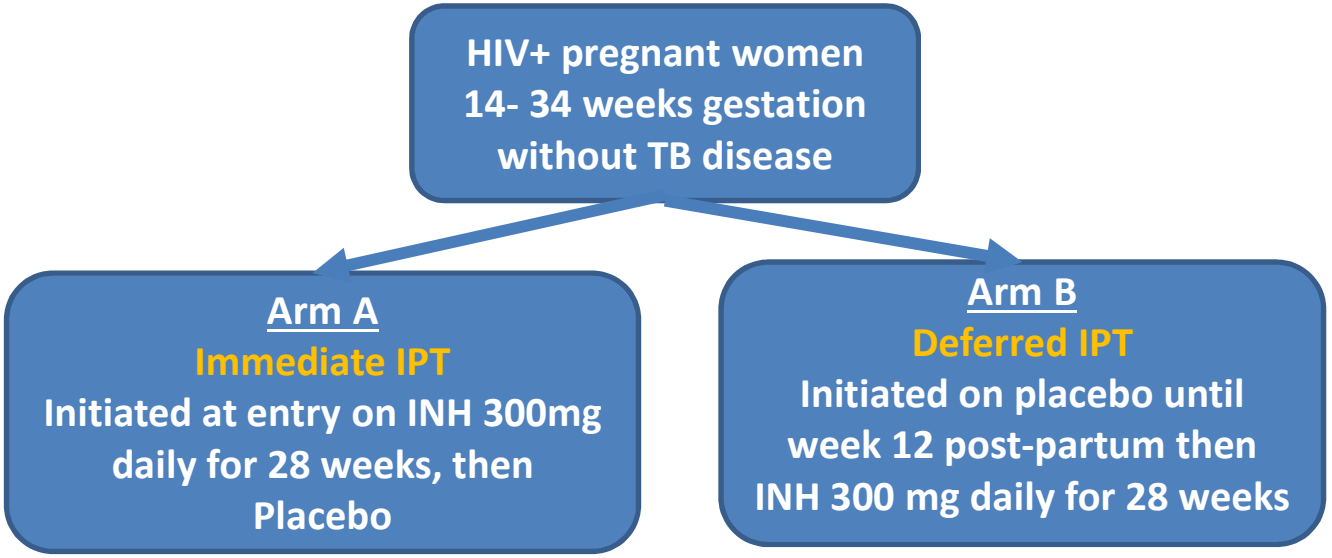
3HP vs. Periodic 3HP vs. 6H in HIV-positive individuals

- **Part A: single round of 3HP vs. 6 months of INH:**
  - Primary endpoint: self-reported treatment completion
- **Part B: 3HP given once per year x 2 years vs. 3HP given only once**
  - Primary endpoint: confirmed TB (culture, Xpert, smear) or clinical TB
- **Study sites: South Africa, Ethiopia, Mozambique**
- **Status: enrollment complete; follow-up through September 2019**

Aurum Institute
clinicaltrials.gov; updated May 8, 2018

TB APPRISE: TB Ante vs. Postpartum Prevention with INH in HIV Seropositive Mothers and their Exposed Infants

- **Study Design**: **Phase IV multicenter, randomized, double-blind, placebo-controlled, non-inferiority trial**
- **Population**: HIV-positive pregnant women ≥ 14 - ≤ 34 weeks gestation who live in a **high TB burden area**, defined as TB prevalence ≥ 60/100,000 population



Study drugs (INH vs. placebo), open label pyridoxine (vitamin B_6) and open label prenatal multivitamin terminated at 40 weeks post-partum

End of follow-up: 48 weeks post-partum

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

TB APPRISE: TB Ante vs. Postpartum Prevention with INH in HIV Seropositive Mothers and their Exposed Infants

Characteristic	Immediate INH	Deferred INH
Median age (years)	29	29
Median BMI	26	26
IGRA-positive (%)	29%	30%
Median baseline CD4	491	496
ART use (%)	99.8%	100%
EFV/ TDF / FTC or 3TC	84%	84%
NVP / ZDV or TDF / FTC or 3TC	12%	13%
Maternal TB per 100 p-y	0.60	0.59
Maternal deaths per 100 p-y	0.4	0.78
Infant TB per 100 p-y	0.54	0.52
Infant deaths per 100 p-y	2.99	4.42

Gupta A et al. CROI 2018

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Primary Endpoint Analysis

Primary endpoint = First maternal treatment-related Grade ≥ 3 adverse event or permanent drug discontinuation due to toxicity

Outcomes	Arm A Immediate	Arm B Deferred	IR/100 PY	IRD (upper limit of 95% CI)
Primary endpoint: Intent-to-treat	**72/477 (15%)**	**73/479 (15%)**	**15.0 vs 14.9**	**0.1 (4.98)**
Primary endpoint: Per protocol	**64/376 (17%)**	**69/388 (18%)**	**16.0 vs 16.7**	**-0.7 (4.9)**

Non-inferiority margin for the primary endpoint: 5/100 PY

Gupta A et al. CROI 2018

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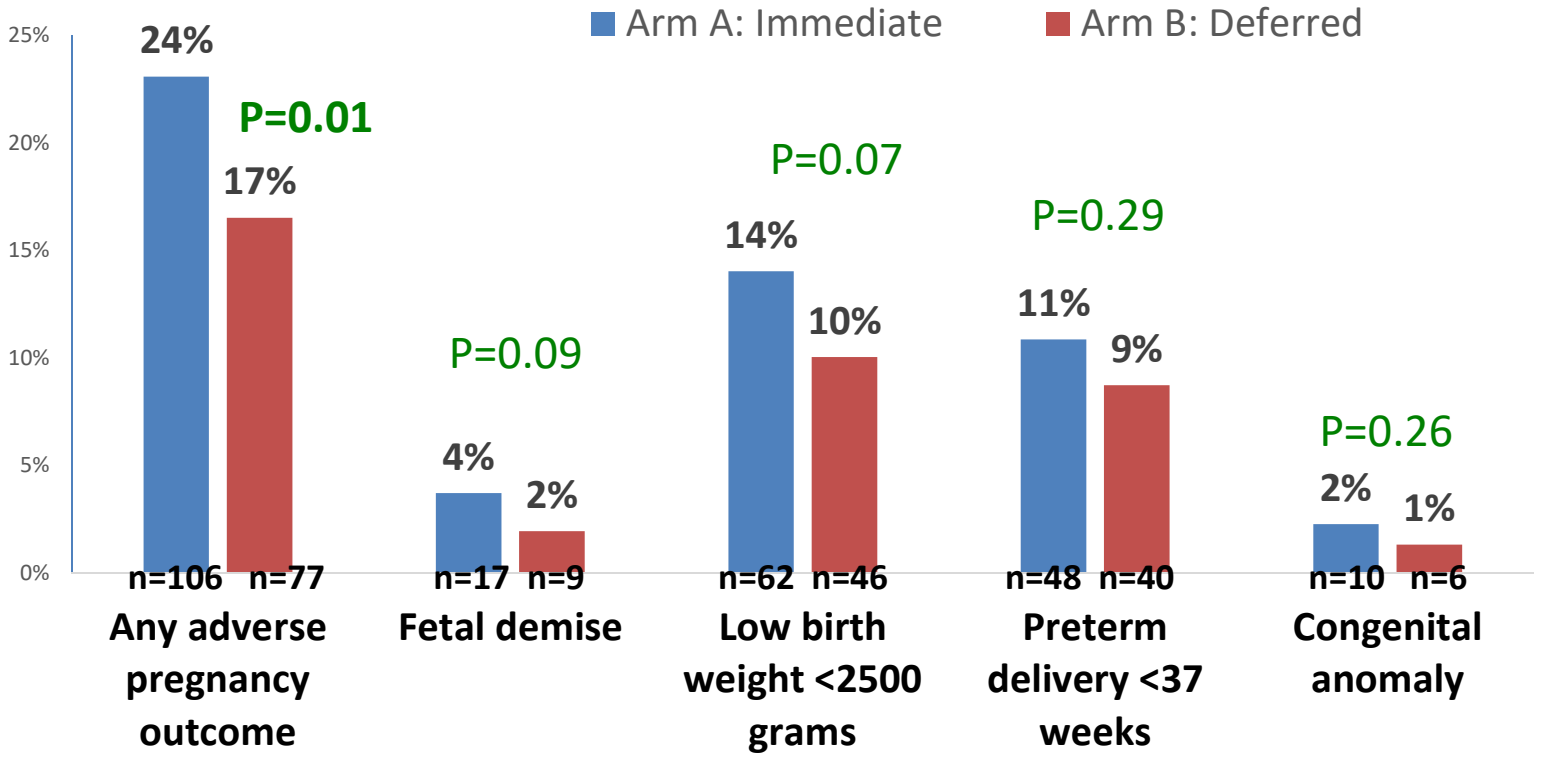
Secondary Outcomes: Adverse Pregnancy Outcomes

- 926 deliveries (460 in immediate arm vs 466 in deferred arm)
  - 915 singletons, 11 twins for total of 937 fetuses/infants
  - 26 stillbirths (fetal demise)
  - 2 abortions (1 spontaneous, 1 induced)
  - 909 live births



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Conclusions—TB APPRISE

- Immediate and deferred IPT had similar safety based on the primary endpoint
- Immediate IPT was associated with a higher risk of adverse pregnancy outcomes
- Maternal and infant TB rates were low in both study arms
- Current WHO guidelines for IPT in pregnant HIV-infected women on ART and living in high TB incidence settings need to be re-evaluated.

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Overall Conclusions

- Recent clinical trials support use of 3-4 month rifamycin-based treatment of latent *M. tuberculosis* infection due to higher treatment completion rates and tolerability compared to isoniazid
  - More data needed with 4R in HIV+ persons
- Ultra-short course regimens hold great promise
- Antiretroviral therapy and treatment of latent *M. tuberculosis* infection independently decrease TB risk in HIV-positive persons
- The optimal approach to confer long-term protection against developing TB among HIV+ persons in high TB incidence settings is under investigation