# Rationale

- Pregnant/postpartum women with latent TB infection have a high risk of developing active TB, especially those with HIV.[1]
- The World Health Organization recommends daily isoniazid (INH) preventive therapy for people living with HIV, including in pregnancy.[2]
  - Results from P1078 raise concerns about safety of 6m of daily INH in pregnancy.[3]
- The newer regimen of 3 months of weekly INH + rifapentine (RPT) (3HP) has not been tested in pregnancy.
  - Improved completion rates/decreased hepatotoxicity in HIV-1-infected populations and children.[4-6]
- **The intent of this study was to provide data needed to extend use of this new regimen to pregnant women.**
  - Determine the impact of pregnancy on RPT pharmacokinetics (PK)
  - Compared to historical controls AND by trimester and HIV status.

*[1]Zenner AJRCCM 2011; [2]WHO LTBI 2018; [3]Gupta, NEJM 2019; [4]Sterling NEJM 2011 &[5]AIDS 2016; [6]Villarino JAMA 2015*

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# Primary Objectives

- To estimate the population PK of RPT and desacetyl-RPT (desRPT) in pregnant (2nd and 3rd trimester) and postpartum women who are receiving 3HP (900mg INH + 900mg RPT once-weekly)
  - Hypothesis: Clearance within 25% of non-pregnant cohorts

- To estimate the incidence of serious adverse events (SAEs) related to 3HP for 12 weeks in pregnant women

- To describe the infant safety outcomes among infants born to women receiving 3HP

# Study Population

## Key Inclusion Criteria:

- Gestational age:
  - Cohort 1: 14 to <28 wks
  - Cohort 2: 28 to <34 wks
- One of the following TB risk factors:
  - Household contact with pulmonary TB patient
  - HIV-infected with positive TST or IGRA at any time
- HIV-infected women on EFV +2NRTI regimen
- ALT ≤3x ULN
- Total bilirubin ≤2.5 x ULN

## Key Exclusion Criteria:

- Active TB (within 2 years)
- Treated latent TB
- Exposure to drug-resistant TB

*Key: ALT= alanine aminotransferase; EFV= Efavirenz; IGRA= interferon gamma release assay; NRTI= nucleoside reverse transcriptase inhibitors; TST= tuberculin skin test; ULN= upper limit of normal*

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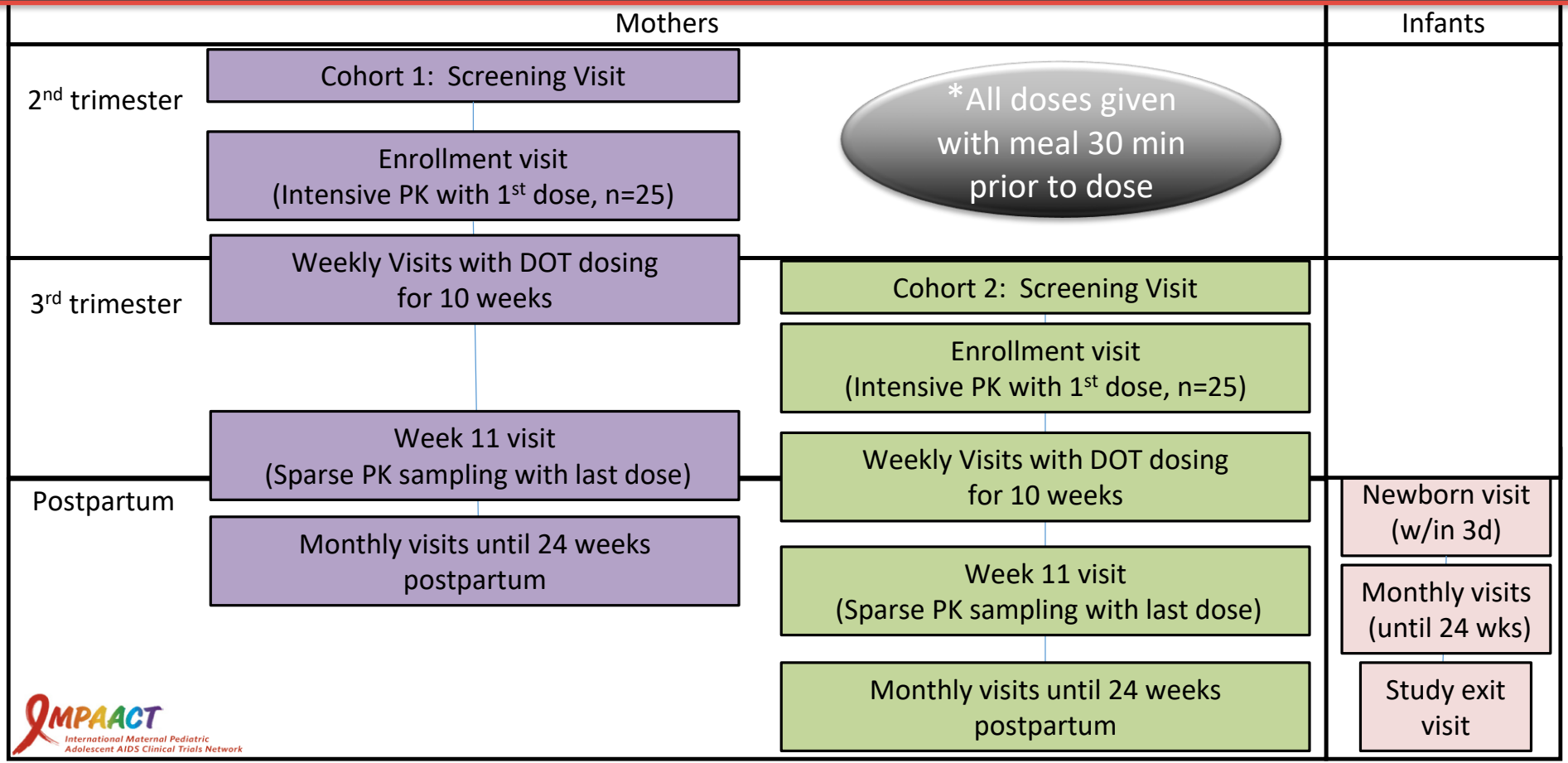
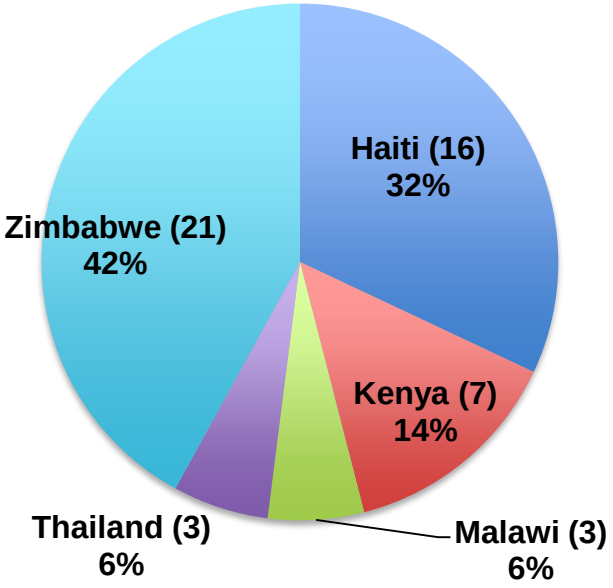
# Phase I/II Study Design



# Study Sites
## (Enrollment: March 2017- June 2018)

**Enrollments by country (n=50)**

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# Results: Baseline Maternal Characteristics

| Characteristic | Total (n=50) | Cohort 1 (n=25) | Cohort 2 (n=25) |
|---|---|---|---|
| Black, Non-hispanic | 47 (94%) | 24 (96%) | 23 (92%) |
| Median Age, yrs (IQR) | 27 (20-32) | 26 (22-33) | 27 (20-31) |
| Median gestational age, weeks (IQR) | 26 (20-30) | 20 (16-24) | 30 (28-31) |
| HIV-positive | 20 (40%) | 10 (40%) | 10 (40%) |
| Median CD4 count, cells/$mm^3$ (IQR) | 510 (390-877) | 586 (415-846) | 489 (368-952) |
| Weight, kg (IQR) | 61 (56-67) | 59 (55-66) | 61 (58-67) |
| Median mid upper arm circumference, cm (IQR) | 27 (25-30) | 27 (25-31) | 27 (26-29) |
| Median prothrombin time, sec (IQR) | 10 (10-11) | 10 (10-11) | 11 (10-12) |

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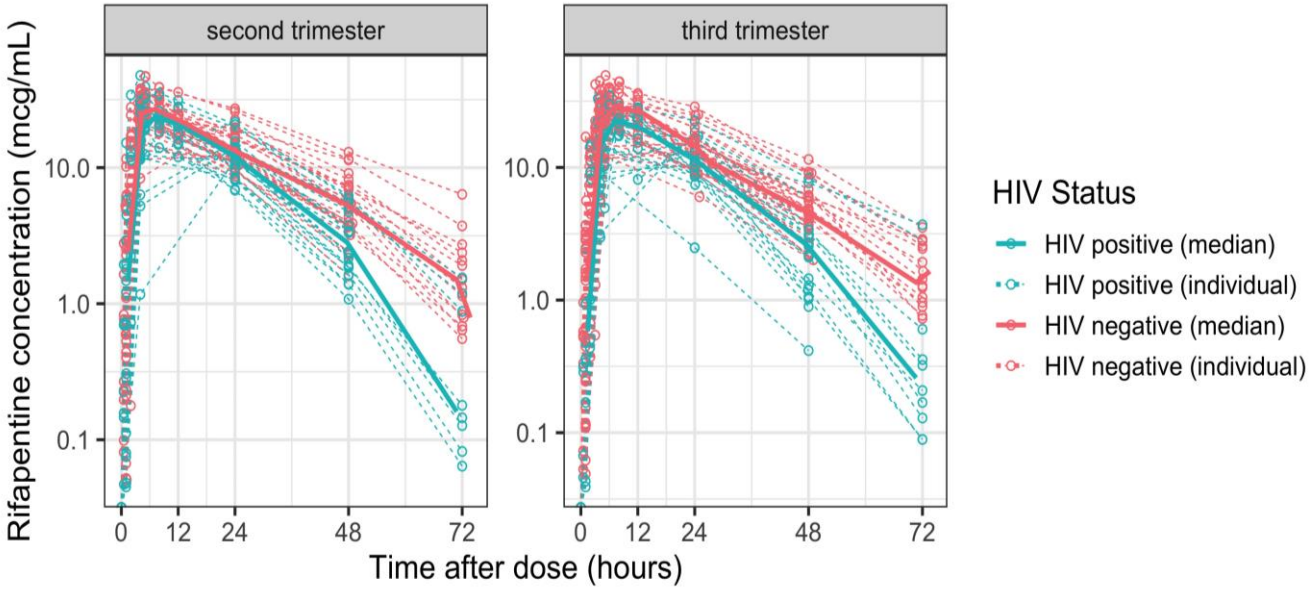
# Effect of HIV on clearance of RPT




Clearance in HIV-positive women was 30% **HIGHER** than HIV-negative women

| Parameter | HIV-positive | HIV-negative | % change vs. HIV- |
|---|---|---|---|
| Clearance (L/hr) | 1.60 (8%) | 1.24 (6%) | ↑29% |
| $AUC_{0-24}$ (mg/L*hr) | 512 (357-794) | 736 (501-1174) | ↓30% |

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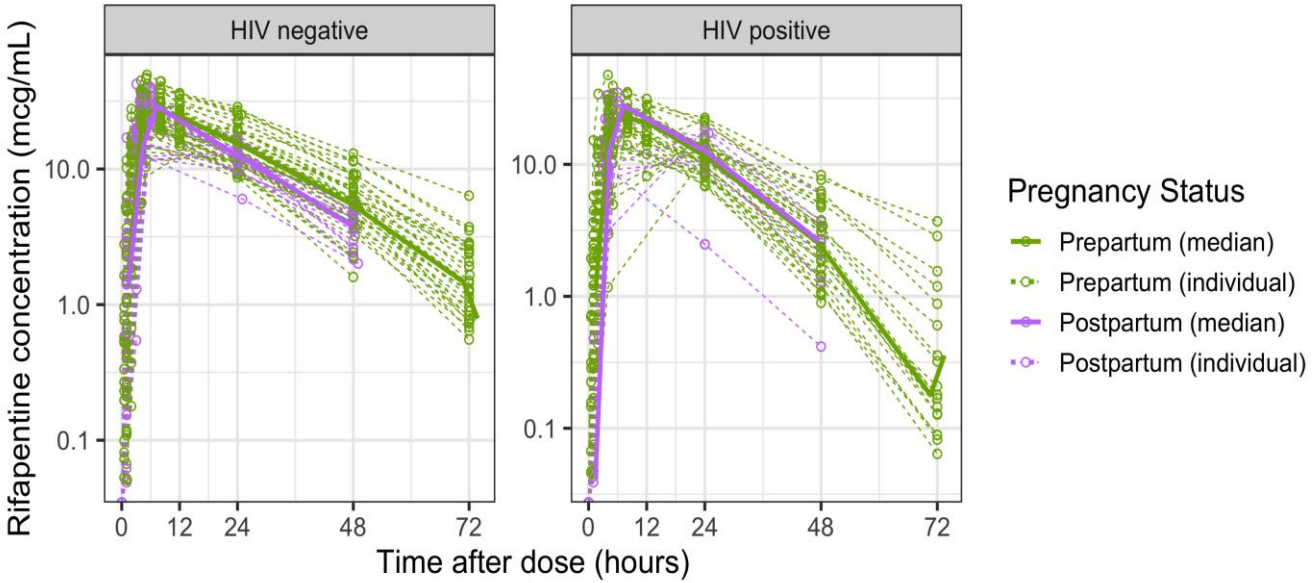
# Effect of pregnancy on clearance of RPT




Postpartum clearance was 35% **HIGHER** in HIV-negative women but not HIV-positive women

| Status | Antepartum | Postpartum | % change vs. pregnancy |
|---|---|---|---|
| HIV-positive | 1.60 (8%) | 1.61 (13%) | 0% |
| HIV-negative | 1.24 (6%) | 1.68 (7%) | ↑35% |

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# Clearance comparable to non-pregnant historic controls

| | IMPAACT 2001 | | PREVENT-TB[1] | TBTC S29B[2] |
|---|---|---|---|---|
| Study population | HIV-positive and HIV-negative pregnant/postpartum women | | HIV-negative children & adults | HIV-negative adults |
| | HIV pos PP | 1.61 (13%) | | |

**NO** dose change required for RPT in pregnant and postpartum women

"Acceptable" = median CL/F is within 25% of CL/F of non-pregnant historical controls

PREVENT TB: 1.47 + 0.25 (2.32) = **1.83 L/hr** 1.47 – 0.25 (1.47) =**1.1 L/hr**

TBTC S29B: 1.18 + 0.25 (1.18) = **1.47 L/hr**

*[1] Weiner, J Peds Infect Dis 2014; [2]Savic AAC 2014;*

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# AUC comparable to non-pregnant controls

| | IMPAACT 2001 | | PREVENT-TB[1] | | TBTC S29B[2] |
|---|---|---|---|---|---|
| AUC (mcg*h/mL) | HIV neg preg | 736 (501-1174) | Children | 759 (375-1186) | 525 (276-979) |
| | HIV neg PP | 618 (415-789) | Adults | 553 (326-931) | |
| | HIV pos preg. | 512 (357-794) | | | |
| | HIV pos PP | 512 (478-629) | | | |

- HIV-positive non-pregnant adults have up to 30% decrease in AUC compared to HIV-negative.[3]

*[1] Weiner, J Peds Infect Dis 2014; [2]Savic AAC 2014; [3]Radtke, CROI 2020 (Abstract#729)*

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# Results: Maternal Safety

- NOT powered for safety
- All 50 enrolled women completed the study regimen.
- No women developed active TB.
- There were no serious adverse events related to study drug.
  - 1(2%) with Grade 2 muscle cramps possibly drug-related at study week 7.
- One death from placental abruption at study week 21.

| Event | Total (n=50) |
|---|---|
| SAE | 5 (10%, CI: 3%, 22%) |
| Abruptio Placentae* | 2 |
| Hypertensive disorders | 3 |
| Postpartum hemorrhage | 1 |
| Death* | 1 |
| Other Grade 3-4 AE | 9 (18%, CI: 9%, 31%) |
| Hematologic | 5 |
| Anemia | 4 |
| Elevated PT | 1 |
| Hypertensive disorders | 1 |
| Still birth* | 1 |
| Premature delivery | 1 |
| Bacterial pneumonia | 1 |

** Same participant*

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# Results: Infant Safety

- 22 infants born to moms who were still on study drug.
- No infants developed active TB.
- No infants had a treatment-related SAE.
  - 2 (4%) with Grade 3 /4 elevated PT, possibly related to study drug.

| Event | Total (n=49) |
|---|---|
| *SAE* | 6 (12%) |
| Neonatal sepsis | 4 |
| Hyperbilirubin*# | 2 |
| Respiratory distress* | 1 |
| Premature birth (29 wks)* | 1 |
| Anemia of prematurity* | 1 |
| Small for gestational age# | 1 |
| Subgaleal hematoma# | 1 |
| *Adverse birth outcomes* | |
| Premature birth | 5 (10%) |
| Low birth weight | 4 (8%) |

**# Represent same participant*

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# Conclusions

1. There is no dose adjustment of RPT required in pregnancy.

2. In women with HIV on EFV, clearance of RPT was higher than expected during pregnancy.
   - Exposures remained in the therapeutic range
   - Need studies of RPT and other ART options (e.g. DTG) in pregnancy to see if this effect is from HIV or EFV, specifically

3. Safety and tolerability data for 3HP in pregnancy are encouraging
   - Need larger studies to definitively characterize safety

4. PK data from infants and breast milk coming soon

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***Women and infants in the study***

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SANOFI

# Questions?

Please email me!
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