TB APPRISE: Phase IV Randomized Double-blind Placebo-controlled Trial to Evaluate the Safety of Immediate (Antepartum-initiated) vs. Deferred (Postpartum-initiated) Isoniazid Preventive Therapy among HIV-infected Women in High TB Incidence Settings

IMPAACT P1078

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Disclosures

- Amita Gupta has no financial disclosures

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Background

- TB is the #1 infectious disease killer globally, surpassing HIV
- Pregnancy/postpartum and HIV increase the risk of TB
  - Many negative impacts of maternal TB (mortality, adverse pregnancy outcomes, Infant TB, HIV transmission)
- Isoniazid (INH) preventive therapy (IPT) + antiretroviral therapy (ART) recommended by WHO for HIV-infected persons (STRONG evidence)
  - But quality of evidence is WEAK for pregnant and postpartum women
  - Pregnant women excluded from IPT/TB prevention trials
- INH associated with increased hepatotoxicity in pregnant and postpartum women from retrospective data
- INH associated death 0.001% to 0.1%
- Physiologic changes of pregnancy impact drug metabolism, safety, efficacy
- **The safety, efficacy, and optimal timing of IPT for HIV-positive pregnant women on ART is unknown**

WHO Global TB Report 2017; DeLuca JAIDS 2009;Mathad CID 2012; Gupta JID 2011; Pillay Lancet ID 2000; Gupta CID 2007; Chin BJOG 2010; Jana NEJM 1999; Zenner AJRCMM 2011WHO Guidelines for LTBI Management 2018; www.nihlivertox.gov; Francks 1989; Mouldings 1989; Brost 1995; Ouyang 2009; Singh 2008; Akolo Cochrane meta-analysis 2010; Frederiksen Semin Perinatol 2001; Anderson Clin Pharmacokinetics 2005; Dooley JID 2016;

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TB APPRISE: IMPAACT P1078 Objectives

- **We hypothesized that IPT can be safely initiated during pregnancy**

Primary Objective

- To compare **overall maternal safety and toxicity** of immediate (started in pregnancy) vs. deferred (postpartum initiated) INH in HIV-infected pregnant women enrolled at ≥ 14 through 34 weeks gestation

Key Secondary Objectives

- To compare **hepatotoxicity**
- To compare **safety and toxicity** of INH exposure ***in utero*** and in study **infants**
- To compare **TB incidence** and **all-cause mortality** in HIV-infected women and their infants

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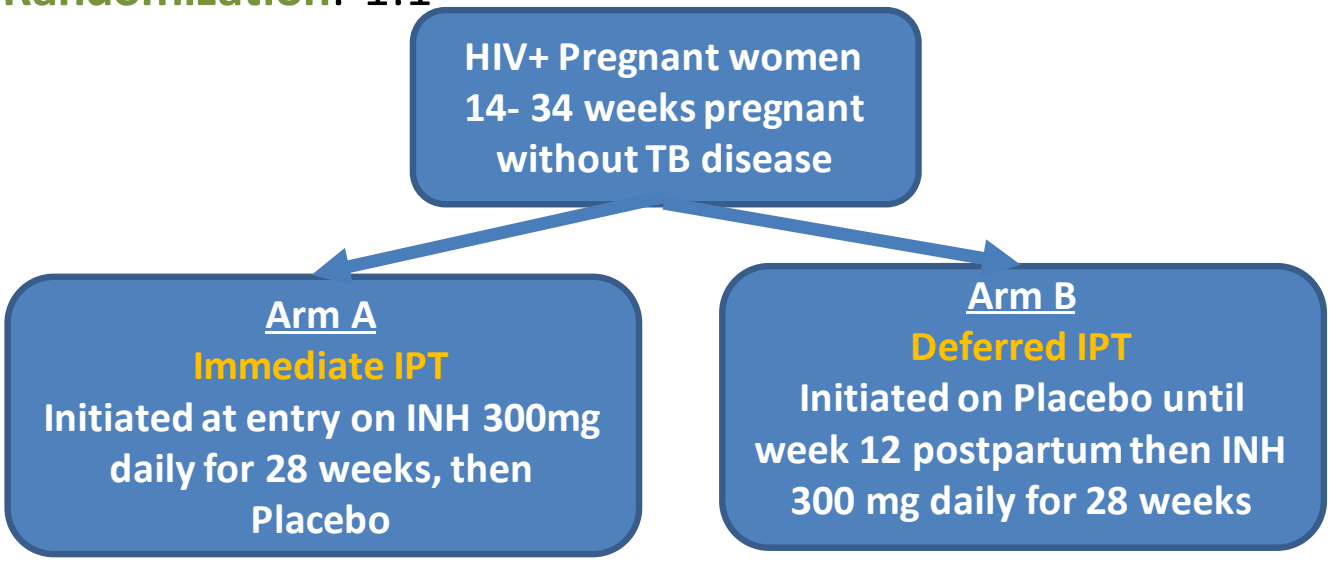
TB APPRISE: IMPAACT P1078 Study Design

- **Design**: **Phase IV multicenter, randomized, double-blind, placebo-controlled, non-inferiority trial**
- **Population**: HIV-infected pregnant women ≥ 14 weeks through ≤ 34 weeks gestation who live in a **high TB burden area**, defined as TB prevalence ≥ 60/100,000 population
- **Randomization**: 1:1



Study drugs (INH/Placebo), open label Pyridoxine (vitamin B_6) and open label prenatal multivitamin terminated at 40 weeks postpartum

End of follow-up: 48 weeks postpartum

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TB APPRISE: IMPAACT P1078 Study Design

- **Stratification**
  - 1) **Gestational age** (14-<24 weeks, 24-34 weeks)
  - 2) **ART use at entry** (Yes/No) – removed as all were on ART
- **Inclusion criteria**
  - **Weight** ≥ 35 kg
  - **Absolute neutrophil count** ≥ 750 cells/mm^3
  - **Hemoglobin** ≥ 7.5g/dL
  - **Platelet count** ≥ 50,000 cells/mm^3
  - **AST, ALT, bilirubin** ≤ 1.25 x ULN
- **Exclusion criteria**
  - Suspected of **having active TB**
  - Reported **recent exposure to TB**
  - **Received TB treatment** >30 days in past year
  - **Recent acute hepatitis**
  - ≥ grade 1 **peripheral neuropathy**
- **Visits**: **Monthly**
  - All women and their infants received **local standard of care for HIV, PMTCT**
  - **Intensified TB case finding** with WHO symptom screening and exam
  - **Monitoring** of signs/symptoms, **safety labs** (LFTs), **peripheral neuropathy** screening

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Study Endpoints

- Independent endpoint review committee
- DSMB monitored the study
- **Primary safety endpoint:**
  - **Occurrence of first treatment-related maternal adverse events (AE) ≥ grade 3 or permanent drug discontinuation due to toxicity**
  - Supplementary to the primary maternal safety endpoint: **All cause Grade 3 or higher AEs**
- **Secondary endpoints:**
  - **Maternal**
    - Maternal hepatotoxicity
    - Maternal TB (confirmed/probable)
    - Maternal death
  - **Infant**
    - All cause Grade 3 or higher AEs
    - Infant TB
    - Infant Death
  - **Adverse pregnancy outcomes**
    - In utero fetal demise/stillbirths
    - Low birth weight
    - Preterm delivery
    - Congenital anomalies

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Statistical Considerations

- **Non-inferiority margin (NIM):**
  - Between-arm difference in primary endpoint incidence rates (IR) of **NIM = 5/100 person-years (PY), in Deferred IPT (arm B)** (based on reports in non-pregnant HIV-positive adults)
    - 90% power

- **Primary Analysis:**
  - **Intent-to-treat** (include all women randomized to their treatment arm); **supplementary per-protocol analysis** (include all women who completed INH/Placebo up to week 40 postpartum)
  - Conclude non-inferiority if **upper bound of 95% CI for between-arm difference in IR < NIM**

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Accrual and Study Sites by Country

956 Enrolled

R

n=477

n=479

Immediate INH

ITT n=477

Per protocol n=376

Deferred INH

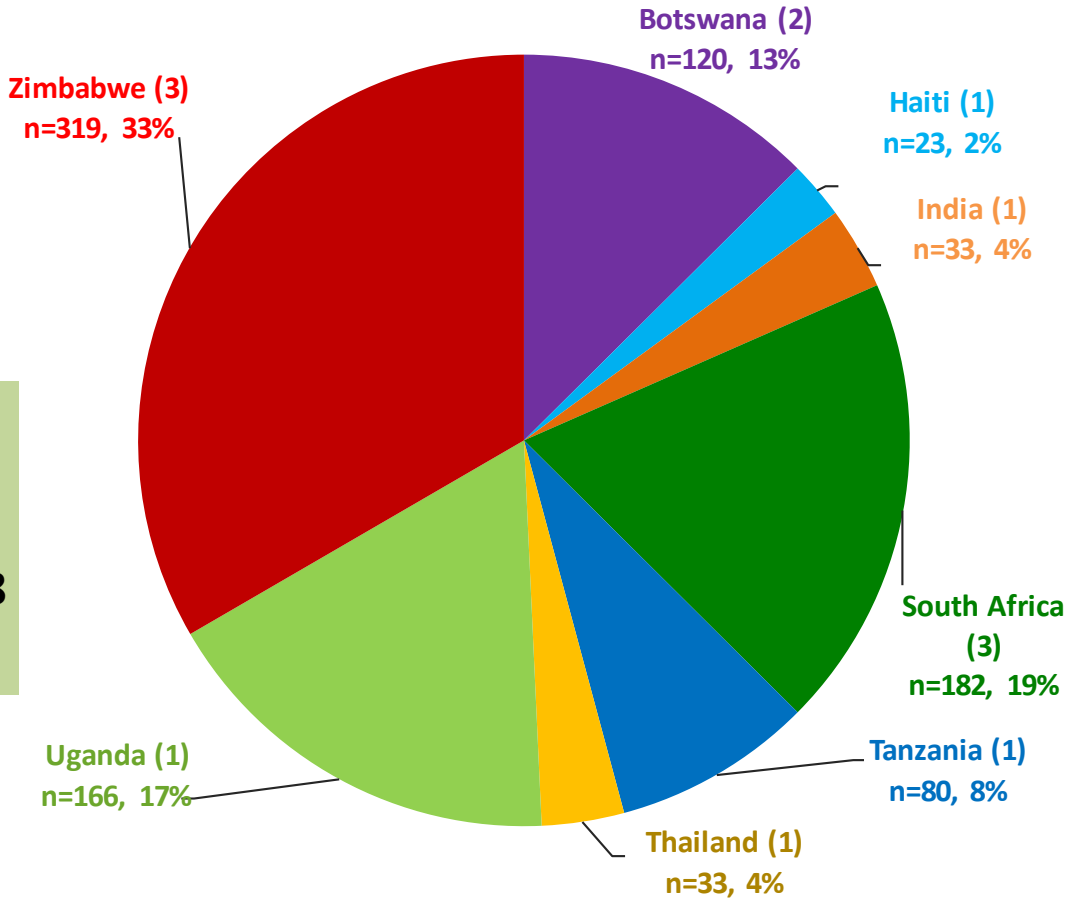
ITT n=479

Per protocol n=388

13 sites (8 countries)

First participant randomized Aug 19, 2014

Fully accrued on April 4, 2016



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Baseline Maternal Characteristics

Characteristics	Immediate (n=477)	Deferred (n=479)	Total (n=956)
Median age, years	29	29	29
Race			
Black	444 (93%)	444 (93%)	888 (93%)
Asian	32 (7%)	35 (7%)	67 (7%)
Other	1 (0%)	0 (0%)	1 (0%)
Gestational age category, weeks			
14 - <24	161 (34%)	160 (33%)	321 (34%)
24 – 34	316 (66%)	319 (67%)	635 (66%)
Median CD4 count, cells/uL	491	496	493
HIV-1 RNA <200 copies/mL	391 (82%)	385 (80%)	776 (81%)
HAART			
3TC/FTC+TDF+EFV	405 (85%)*	409 (86%)	814 (85%)
3TC+AZT/TDF+NVP	59 (13%)	61 (12%)	120 (13%)
3TC/FTC+ AZT/TDF+LPV/ATV+r	13 (2%)	9 (2%)	22 (2%)
Interferon gamma release assay Positive (Quantiferon Gold-in-tube)	140 (29%)	144 (30%)	284 (30%)
Prior TB	13 (3%)	18 (4%)	31 (3%)
Hepatitis B surface Antigen Positive	15 (3%)	18 (4%)	33 (3%)
Hepatitis C Antibody Positive	5 (1%)	4 (1%)	9 (1%)
Median ALT (SGOT) U/L	14	13	14

*1 was on EFV alone and 1 was on EFV/NVP combination

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Primary Endpoint Analysis

Primary endpoint = First Maternal Treatment-related Grade ≥ 3 AE or permanent drug discontinuation due to toxicity

Outcomes	Arm A Immediate	Arm B Deferred	IR/100 PY	IRD (95% CI)
Primary endpoint: Intent-to-treat	74/477 (15.5%)	73/479 (15.2%)	15.4 vs 14.9	0.5 (-4.4, 5.4)
Primary endpoint: Per protocol	66/376 (17.6%)	69/388 (17.8%)	16.5 vs 16.7	-0.2 (-5.8, 5.4)

Primary analysis on primary endpoint: **Nearly reached NIM of 5/100 PY**

All cause Grade ≥3 maternal AEs: Intent-to-treat	145/477 (30.5%)	136/479 (28.4%)	35.4 vs 31.3	4.2 (-3.6, 12.0)
All cause Grade ≥3 maternal AEs: Per protocol	124/376 (33.0%)	118/388 (30.4%)	36.4 vs 32.1	4.3 (-4.3, 12.9)

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Tabulation of Primary Safety Endpoints

	Treatment group					
	Immediate INH n=477		Deferred INH n=479		Total	
Any Primary Safety Endpoint	**74**	**(15.5%)**	**73**	**(15.2%)**	**147**	**(15.4%)**
Elevated liver function test(s)	27	(5.7%)	31	(6.5%)	58	(6.1%)
Neuropathy peripheral	1	(0.2%)	0	(0%)	1	(0.1%)
Fatigue	0	(0%)	1	(0.2%)	1	(0.1%)
Nausea	1	(0.2%)	0	(0%)	1	(0.1%)
Weakness						(0.1%)
Weight loss						(5.2%)
Hypertension						(0.1%)
Absolute neutrophil						(0.4%)
Type 1 diabetes mellitus	0	(0%)	1	(0.2%)	1	(0.1%)
Oligohydramnios	0	(0%)	1	(0.2%)	1	(0.1%)
Hypertension disorder of pregnancy	6	(1.3%)	2	(0.4%)	8	(0.8%)
Labor onset and length abnormality	2	(0.4%)	3	(0.6%)	5	(0.5%)
Intrauterine growth retardation	0	(0%)	1	(0.2%)	1	(0.1%)
Antepartum hemorrhage	0	(0%)	1	(0.2%)	1	(0.1%)
In utero demise/stillbirth	5	(1.0%)	2	(0.4%)	7	(0.7%)
Multiple attributes	3	(0.6%)	3	(0.6%)	6	(0.6%)

45 permanently discontinued study drug due to toxicity
35 discontinued due to protocol-defined toxicity,
9 due to non protocol-defined low grade toxicity,
and **1 due to death** (due to toxicity)

Hypertension disorder of pregnancy includes eclampsia, pre-eclampsia, and pregnancy-induced hypertension
Labor onset and length abnormality includes preterm labor, preterm delivery, premature rupture of membranes

All cause Grade 3 or 4 Maternal Adverse Events by Treatment Arm

	Treatment Group					
	Immediate (N=477)			Deferred (N=479)		
	Grade			Grade		
Diagnosis/Sign/Symptom/Lab Event	3	4	Total n (%)	3	4	Total n (%)
Participants with at least one event	**116 (24%)**	**29 (6%)**	**145 (30%)**	**105 (22%)**	**31 (6%)**	**136 (28%)**
Any Chemistry	**22 (5%)**	**12 (3%)**	**34 (7%)**	**21 (4%)**	**19 (4%)**	**40 (8%)**
Liver/Hepatic	**19**	**10**	**29**	**18**	**16**	**34**
Any Hematology	**23 (5%)**	**12 (3%)**	**35 (7%)**	**18 (4%)**	**6 (1%)**	**24 (5%)**
Any Hematology, RBC	13	9	22	14	4	18
Any Hematology, WBC/Differential	11	3	14	4	2	6
Gastro-Intestinal	7 (1%)	1 (<0.5%)	8 (1%)	6 (1%)	1 (<0.5%)	7 (1%)
Hepatobiliary Disorders (Hepatitis)	1 (<0.5%)	4 (1%)	5 (1%)	0 (0%)	6 (1%)	6 (1%)
Infections & Infestations	**16 (3%)**	**1 (<0.5%)**	**17 (4%)**	**14 (3%)**	**0 (0%)**	**14 (3%)**
Nervous System	4 (1%)	0 (0%)	4 (1%)	4 (1%)	1 (<0.5%)	5 (1%)
Peripheral Neuropathy	1	0	1	0	0	0
Pregnancy, Puerperium & Perinatal	**36 (8%)**	**5 (1%)**	**41 (9%)**	**37 (8%)**	**2 (<0.5%)**	**39 (8%)**
Induced abortions	1	0	1	0	0	0
Spontaneous abortions	2	0	2	0	0	0
Hypertension disorders of pregnancy	10	2	12	8	1	9
Prolonged labor	8	0	8	8	0	8
In utero demise/stillbirth	15	1	16	8	1	9
Skin	**1 (<0.5%)**	**0 (0%)**	**1 (<0.5%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**
Other	**60 (13%)**	**6 (1%)**	**66 (14%)**	**50 (10%)**	**7 (1%)**	**57 (12%)**

Other Maternal Safety Outcomes

Outcomes	Arm A Immediate	Arm B Deferred	IR/100 PY	IRD (95% CI)
All-cause hepatotoxicity	29/488 (6%)	34/479 (7%)	5.8 vs 6.7	-0.9 (-4.0, 2.2)
Permanent discontinuation due to toxicity	17/477 (4%)	28/479 (6%)	3.3 vs 5.5	-2.1 (-4.7, 0.4)
Death	2/477 (0.4%)	4/479 (0.8%)	0.4 vs 0.8	-0.4 (-1.3, 0.6)

No significant differences in maternal safety by treatment arm

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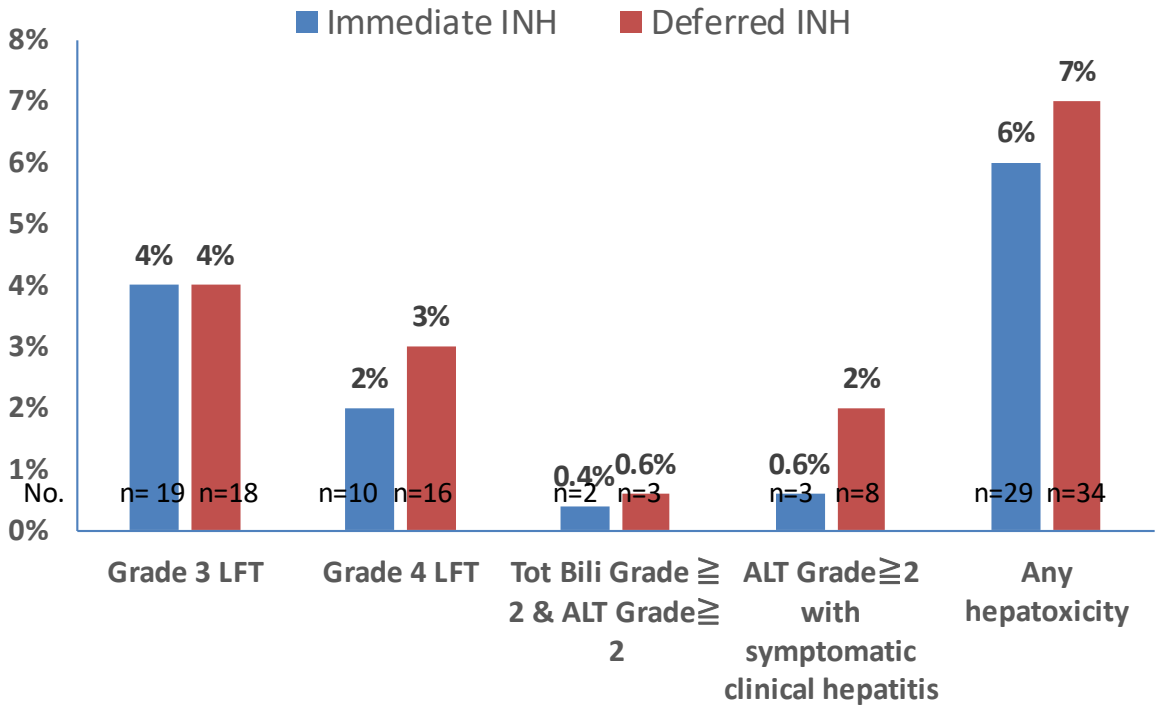
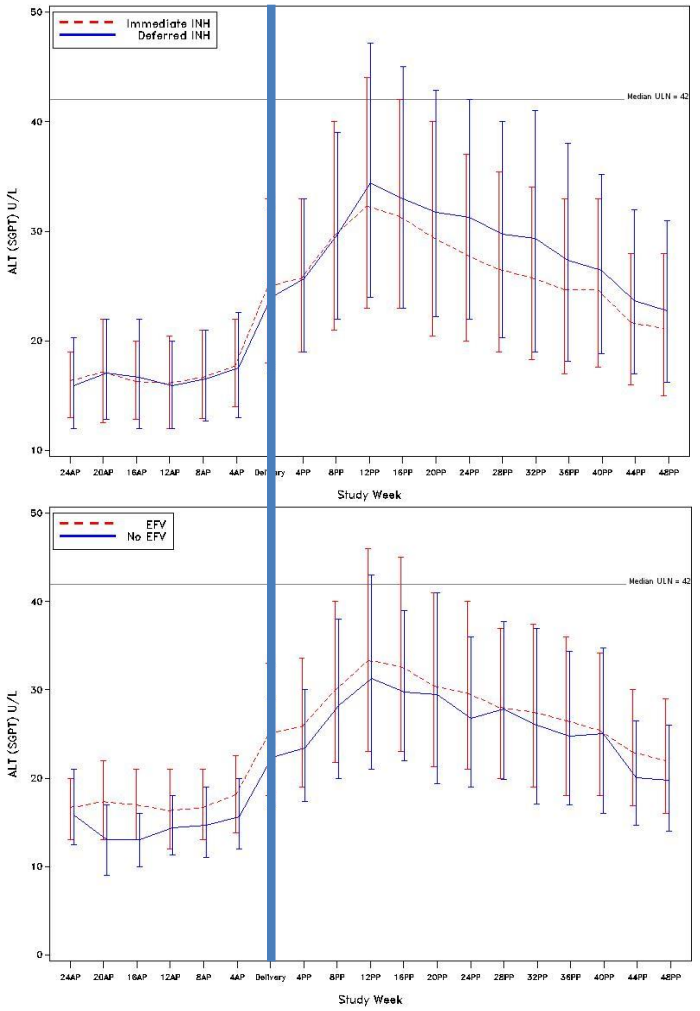
Maternal Hepatotoxicity by Treatment Arm and Median ALT (SGPT) U/L by study week



Delivery



No difference by Arm but Higher LFTs observed after delivery irrespective of whether on IPT or type of ART

Maternal Deaths, n=6

	Immediate IPT		Deferred IPT			
	1	2	3	4	5	6
Location	Zimbabwe	Botswana	Zimbabwe	Tanzania	Tanzania	Tanzania
Age (yrs)	34	38	27	35	24	33
CD4	459	469	402	609	431	553
GA at entry (weeks)	33	21	31	26	26	30
Postpartum (PP) week at death	12 weeks	40 weeks	5 weeks	19 weeks	7.5 weeks	5.5 weeks
Time on INH	13 weeks (4 AP & 9 PP)	28 weeks (20 AP, 8 PP)	Never started	1 week PP	Never started	Never started
ART regimen initiated	TDF/3TC/EFV Started 1 week prior to entry	TDF/FTC/EFV Started 2.5 years prior to entry	TDF/3TC/EFV for 4 months prior to entry	TDF/3TC/EFV + COT 14 months prior to entry	TDF/3TC/EFV started 3 weeks before entry	TDF/3TC/EFV started 1 month before entry
Death cause	Fulminant hepatitis **Related**	Bacterial sepsis **Not related**	Fulminant hepatitis **Not related**	Fulminant hepatitis **Related**	Hepatitis **Not related**	Pneumonia **Not related**

4 deaths due to hepatotoxicity, 2 deaths related to INH and 2 not (?Efavirenz or other culprit)

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Maternal Off Study Reasons

Review of initial two maternal deaths by DSMB resulted in request to have a participant letter which provided more explicit information about signs and symptoms of hepatotoxicity and risk of death from INH and ARVs

	Immediate IPT	Deferred IPT	Total
Completed study	389 (82%)	396 (83%)	785 (82%)
Eligibility Failure	1 (<1%)	1 (<1%)	2 (<1%)
Death	2 (0%)	4 (1%)	6 (1%)
Withdrew consent prior to study completion	**43 (9%)**	**34 (7%)**	**77 (8%)**
Participant not willing to adhere to study requirements	2 (0%)	9 (2%)	11 (1%)
Study team not able to contact participant	18 (4%)	20 (4%)	38 (4%)
Participant not able to get to clinic	22 (5%)	15 (3%)	37 (4%)

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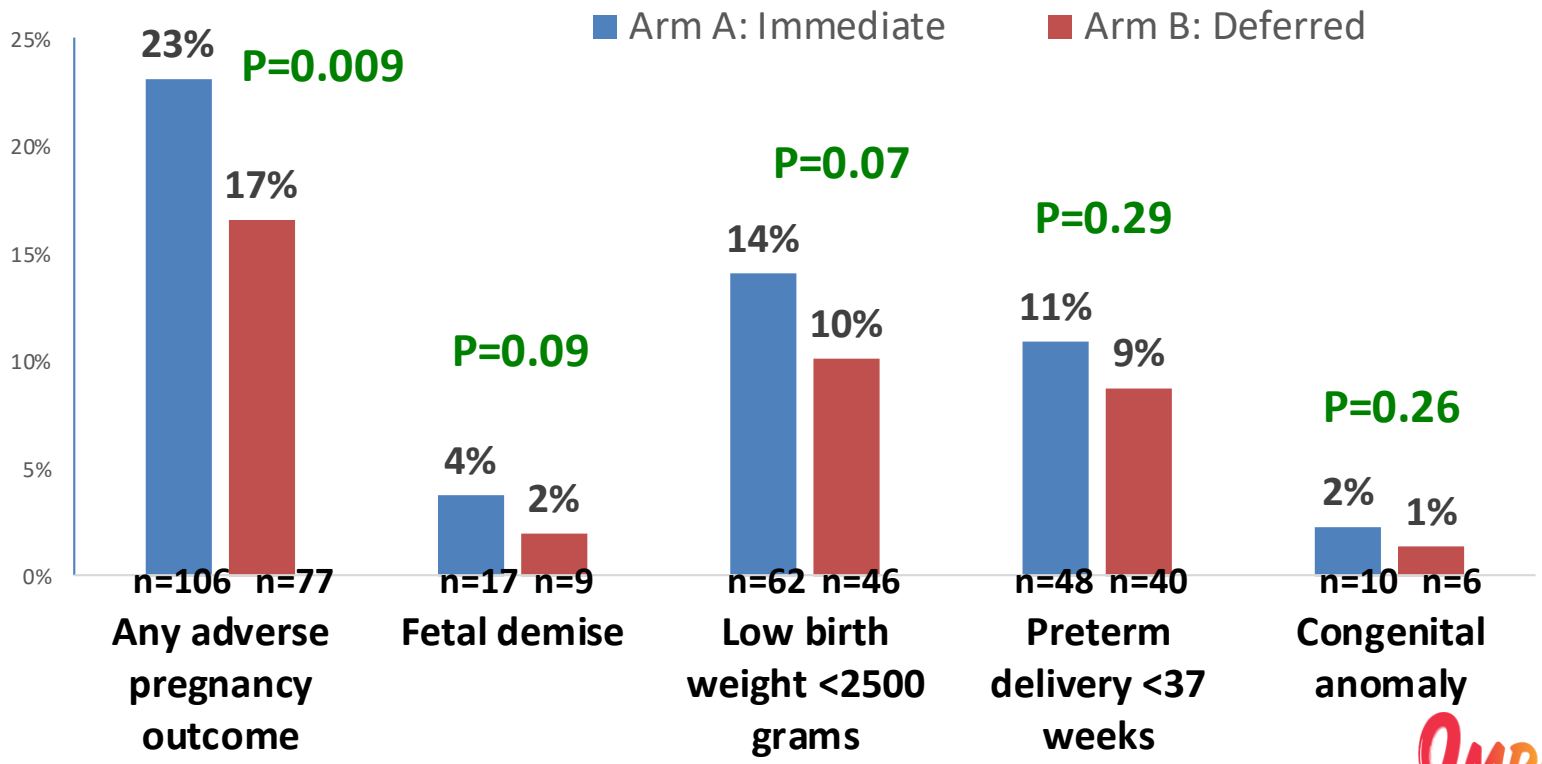
Secondary Outcomes: Pregnancy and Birth Outcomes

- 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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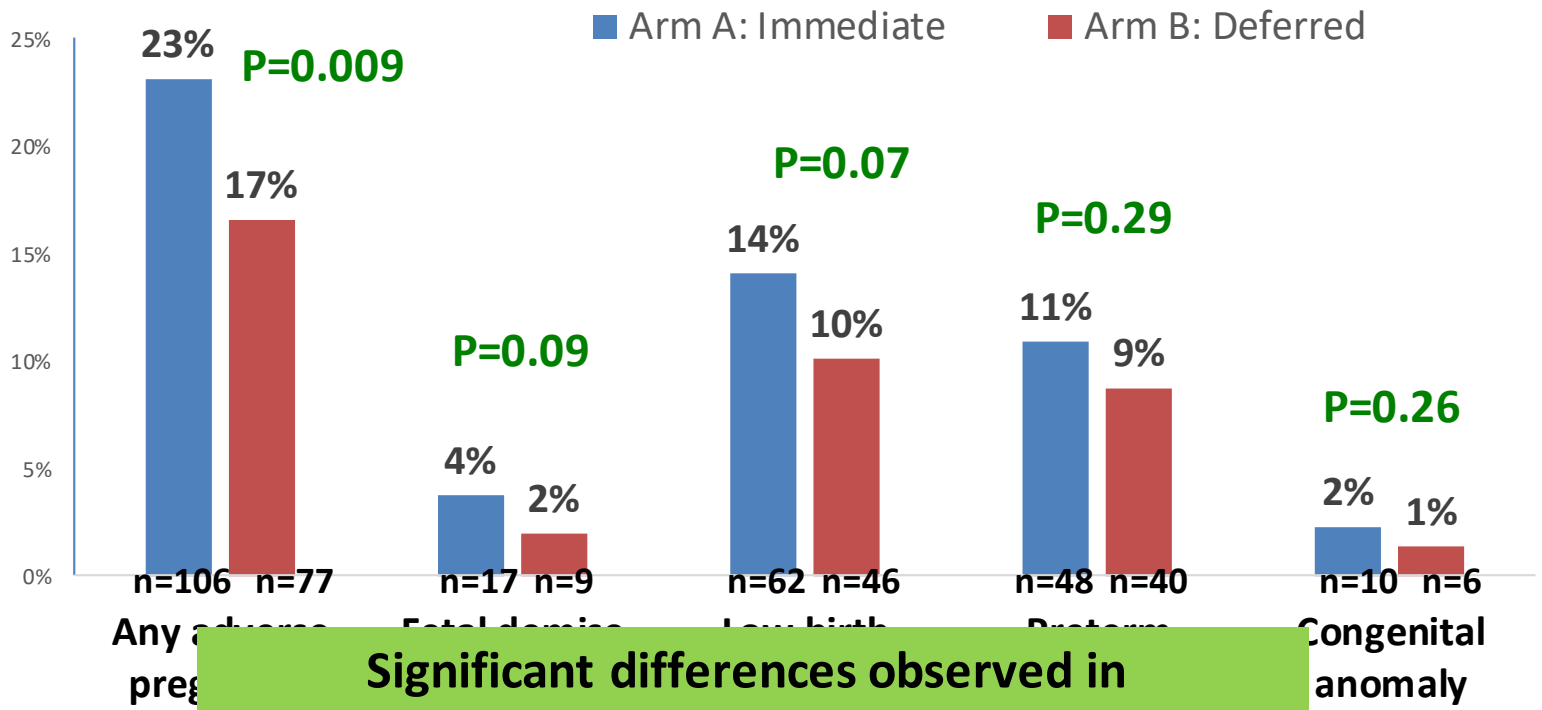

Significant differences observed in Adverse Pregnancy Outcomes by treatment arm

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Secondary Outcomes: Infant Safety

		Treatment Group			
Infant Safety Event	**Category**	**Immediate INH (N=445)**	**Deferred INH (N=464)**	**Total (N=909)**	**P-Value***
Grade 3 or 4 AE	Yes	191 (43%)	189 (41%)	380 (42%)	**0.524**
	No	254 (57%)	275 (59%)	529 (58%)	
Hospitalization	Yes	73 (16%)	75 (16%)	148 (16%)	**0.893**
	No	372 (84%)	389 (84%)	761 (84%)	
Death (overall)	Yes	11 (2%)	17 (4%)	28 (3%)	**0.295**
	No	434 (98%)	447 (96%)	881 (97%)	
*Fisher's Exact Test with Mid-P Adjustment					

No significant differences observed in infant safety by treatment arm

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Secondary Outcomes: Maternal-Infant TB outcomes

Outcome	Arm A Immediate	Arm B Deferred	IR/100 PY	IRD (95% CI)
TB				
Maternal TB	3/477 (0.6%)	3/478 (0.6%)	**0.6 vs 0.6**	0 (-1.0, 1.0)
Infant TB	0/445 (0%)	1/464 (0.2%)	**0 vs 0.3**	-0.2 (-0.6, 0.2)

4 of 6 maternal TB cases were culture confirmed,
1 of which was INH resistant (immediate arm)

No significant differences observed in Maternal or Infant TB by treatment arm

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Conclusions

- **First randomized trial to our knowledge to focus on TB prevention in HIV-infected pregnant and postpartum women at high risk of developing TB**

- **1) What did we learn from the immediate vs deferred IPT?**

  Higher than expected AEs attributed at least possibly to INH in both arms

  - NIM nearly (but not) reached in primary maternal safety endpoint
  - NIM not reached in all cause Grade 3 or higher maternal AEs
  - We are not able to confirm that INH at pregnancy is safe for the mother but we did not find significant difference in maternal safety profile between the two arms

- **2) Are other maternal and infant safety outcomes different?**

  No, there were no significant differences in any maternal hepatotoxicity, Grade 3 or higher infant AEs, or maternal/infant death by treatment arm

- **3) Are maternal/fetal (adverse pregnancy) outcomes different?**

  Yes, IPT during pregnancy associated with higher risk of adverse pregnancy outcomes

- **4) Does timing of IPT affect TB risk?**

  No, maternal TB rates (0.6/100PY) and infant rates (0.1/100PY) were low in both immediate and deferred IPT in ART era

- **Current WHO guidelines of IPT in pregnancy for HIV-infected women need re-evaluation weighing the risks and benefits**

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The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

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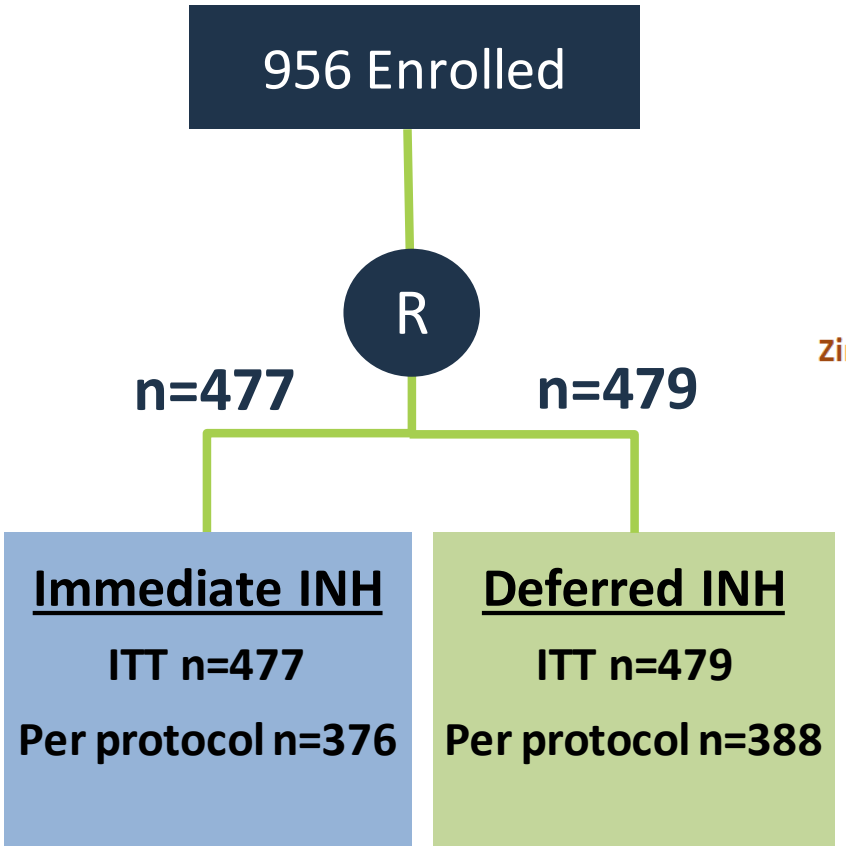
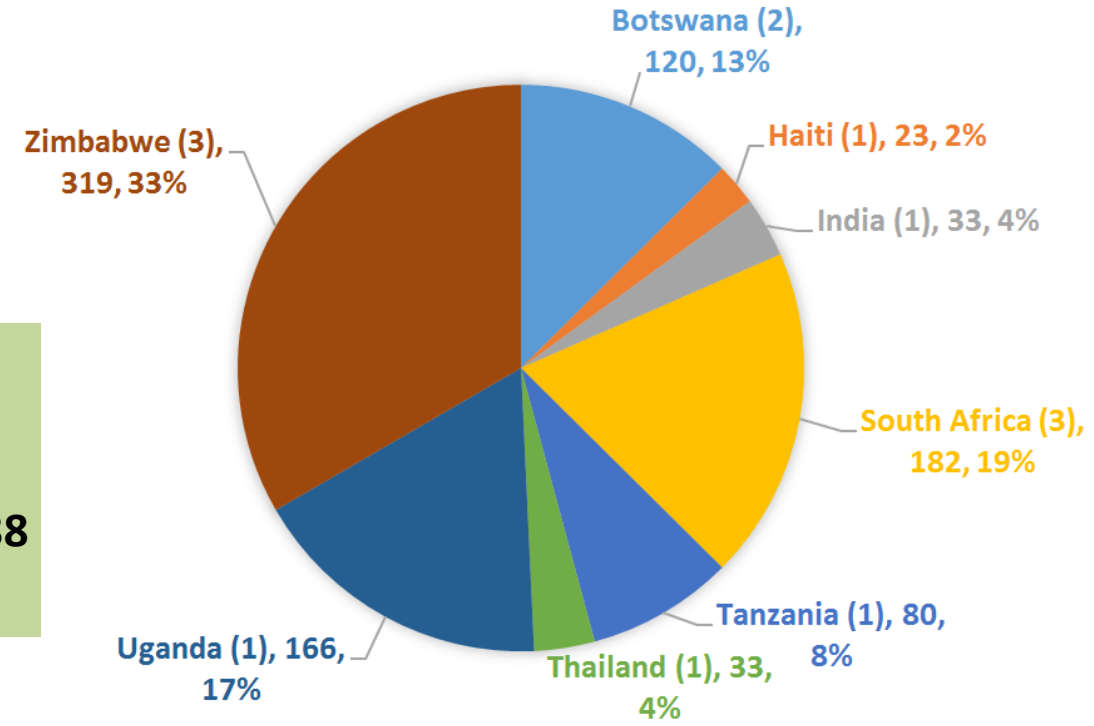
Accrual and Study Sites by Country

13 sites (8 countries)

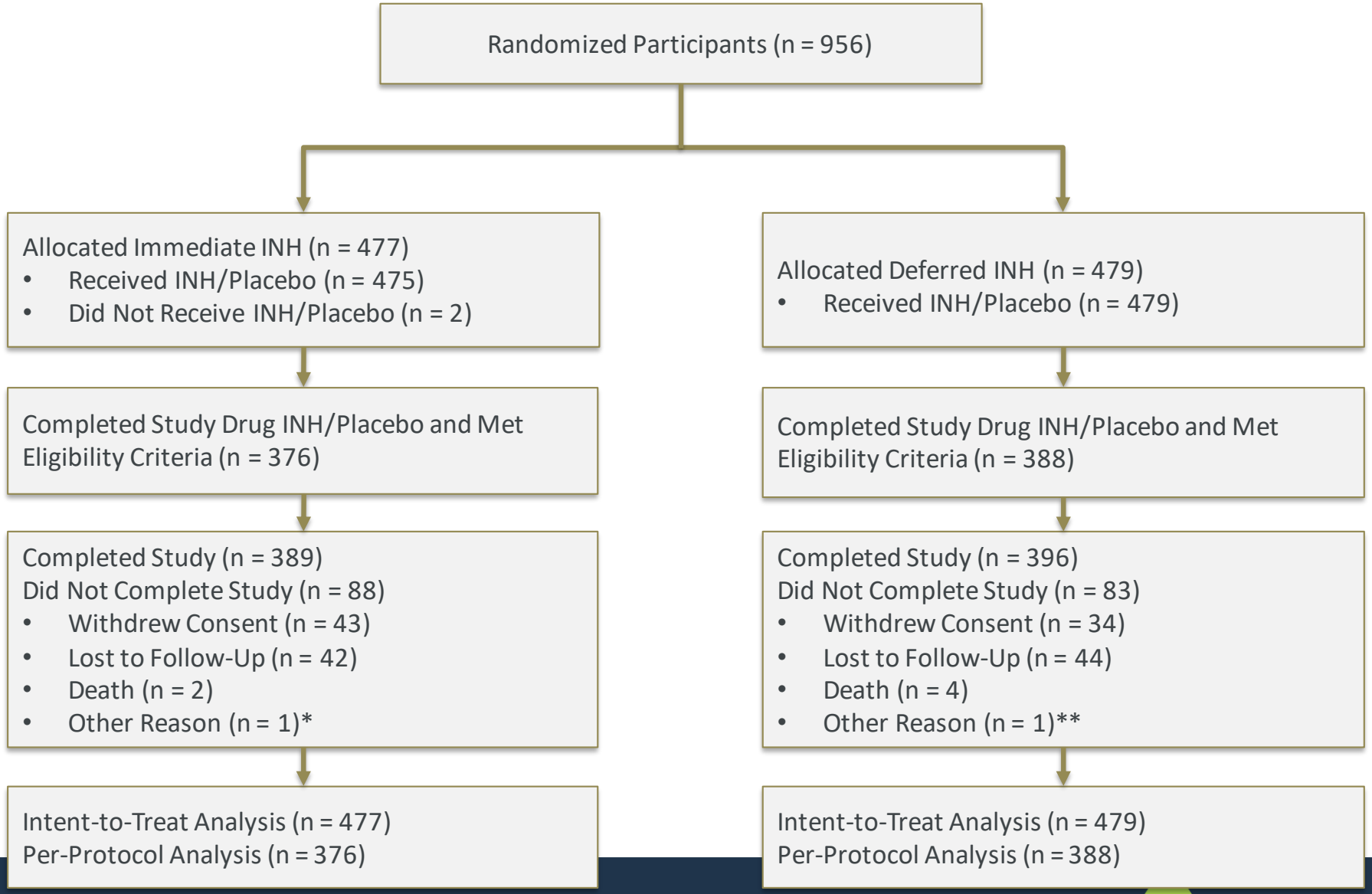
First participant randomized Aug 19, 2014

Fully accrued on April 4, 2016



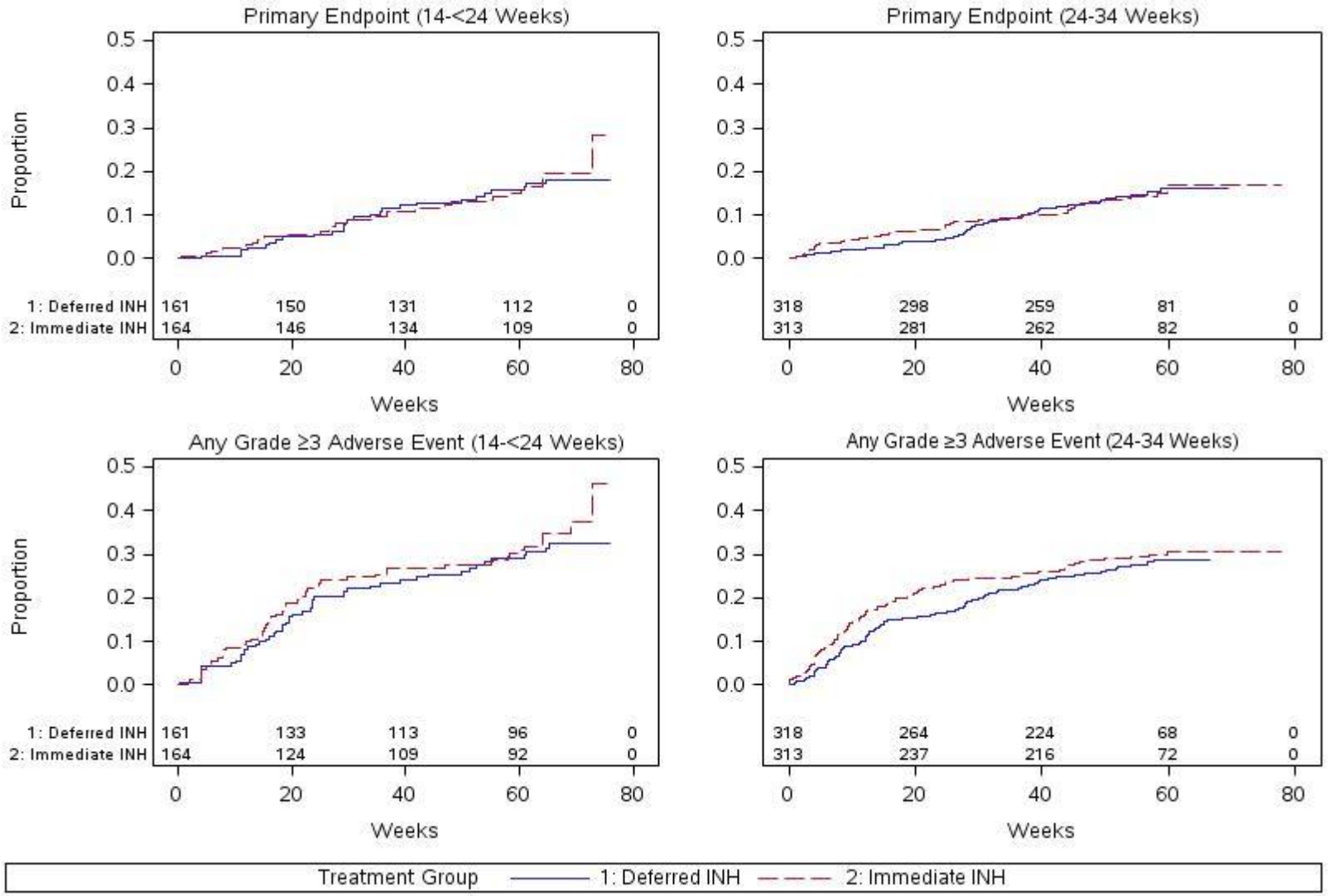


Consort Diagram

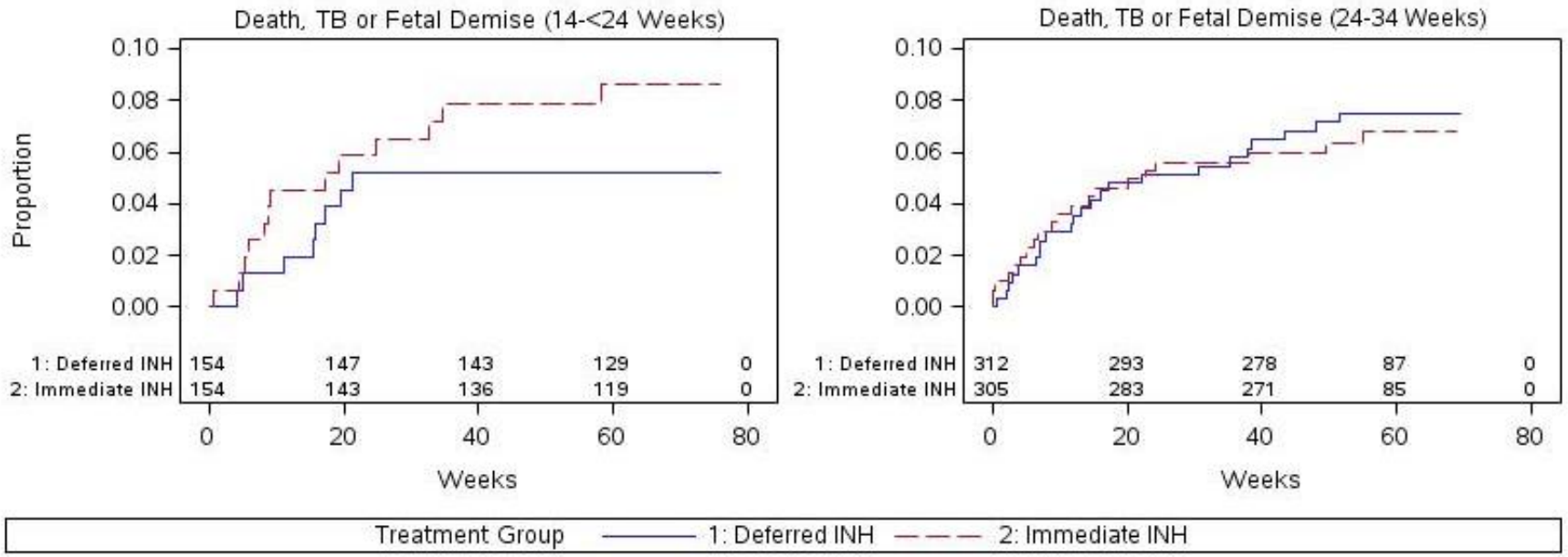


*Participant had active TB at entry that was diagnosed post-entry.
**Participant became ineligible due to co-enrollment in another study.

KM curves of Primary endpoint by GA strata

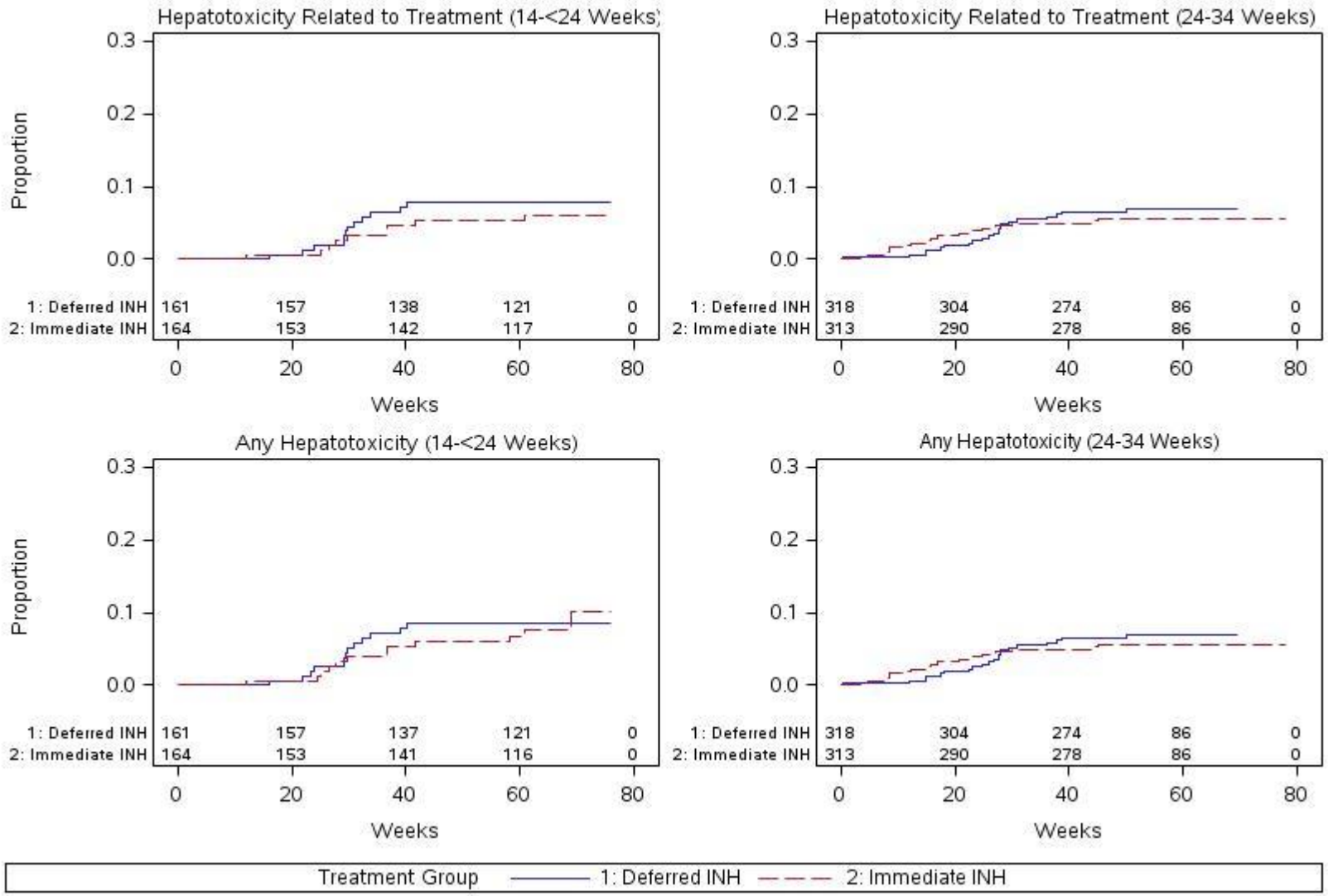


Secondary Outcomes: Maternal-Fetal/Infant Death and TB in composite outcomes by GA strata



No statistical difference but may provide some insight into effect of earlier exposure of IPT

Time to hepatotoxicity by Gestational Age strata



Study regimens

Entry	Week 28 Post-entry Visit	Week 12 Postpartum (PP) visit
Arm A (Immediate) INH 300mg once daily until week 28	Placebo once daily until week 40 PP	Continue current therapy
Arm B (Deferred) Placebo once daily until week 12 PP visit	Continue current therapy	INH 300mg once daily until week 40 PP visit

***Participants also received open-label Vitamin B6 (25 mg) and prenatal multivitamins that contained <5mg B6 with each dose of INH/placebo until week 40 PP visit**

Hepatotoxicity of INH, EFV and INH+EFV

INH

Type	%
Transient LEE	10-20%
>5xULN	3-5%
Symptomatic hepatitis	0.1-1%
Fatal hepatitis	0.001%-0.1%

EFV

Type	%
Transient LEE	?
>5XULN	1-8%
Symptomatic hepatitis	Rare
Fatal hepatitis	Rare

HIV+ INH+ART	
Biochemical	1.45%-5.5% Samandari Lancet 2011 Rangaka Lancet 2014 Martinson 2011

INH and EFV interaction (Dooley JID 2014)
Slow CYP2B6 INH associated with higher EFV Cmin especially if also slow NAT2

Historical knowledge of selected INH studies in US

Study	N	Location	Regimen	Severe Hepatotoxicity Rate	Deaths N
USPHS Kopanoff 1979	13,838	21 health depts USA	INH	1% (LFTs only performed on clinical indication)	8 (6 females, 5 were black)
Franks 1989	3,681 pregnant /postpartum women	USA	INH	0.1% 5/3681 (1030 LTF)	2
Nolan 1999	11,141	Seattle, USA	INH	0.1% Grade >3 (Asx ALT)	0
LoBue 2005	3,788	San Diego, USA	INH	0.3% Grade>3 (>5xULN or 3-5X+sx)	NR
Fountain 2005	3,377	Memphis Shelby County, USA	INH	0.56% Grade>3 (>5xULN AST)	0
Steele 1991	38,257	6 US studies meta-analysis	INH	0.6% (0-2.9% range) clinical hepatitis	NR

Current knowledge of INH and ART in HIV+ studies

Study	N	Location	Regimen	Severe Hepatotoxicity Rate	Deaths N
BOTUSA Samandari 2010	1,768	Botswana	INH w/27% ART	Biochemical 1.45% Clinical 0.4%	1 due to hepatitis
Grant 2010	24,221	South Africa	INH	17/24,220 (0.07%)	1
Rangaka 2014	1,329	South Africa	INH+ART vs ART	Grade 3 or 4 ALT: 3.2% (2.9% discontinued IPT due to ALT)	37 (16 IPT arm of which 8 unknown, 0 liver failure)
Temparano Group 2015	2,056	Ivory Coast	INH + ART in 2 of 4 arms	12/1130 (1%) in IPT arms liver-related Grade 3/4	47 (18 in IPT arms)
Dooley 2015	97 (44 with TB)	South Africa	INH+EFV RIF+EFV	Not reported (PK study)	Not reported

INH Safety in Pregnancy and Post-partum

- FDA category C
- INH data from pre-HIV and pre-HAART era
- Teratogenicity: none based on existing human data
- Possible association of INH and hemorrhagic disease in newborn
- Hepatotoxicity
  - Abnormal liver enzymes (AST/ALT) :1-25%
  - Symptomatic liver disease 5.2 per 1000 patients in a study where 20,838 given INH for 12 mo.
  - **20 deaths in CA, 4 were postpartum women who started INH in pregnancy (Mouldings 1989)**
  - 2.5 fold increased hepatotoxicity and 4-fold increased death in pregnant women but not statistically significant (Francks 1989)
  - Risk factors pregnancy, first 3 months postpartum, possibly HIV, alcohol, underlying liver disease including chronic Hepatitis, age, ?HAART (ATS/CDC/IDSA guidelines)
- Breast milk: safe. Concentration 6.4-25%

Francks 1989; Mouldings 1989; Brost 1995; Ouyang 2009; Singh 2008