Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Gupta A, Montepiedra G, Aaron L, et al. Isoniazid preventive therapy in HIV-infected pregnant and postpartum women. N Engl J Med 2019;381:1333-46. DOI: 10.1056/NEJMoa1813060

Supplementary Appendix

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Supplementary Information on Methods: Justification for Noninferiority Margin, Attribution of Relatedness, Definition of Weight Loss, Handling of Censoring

Justification for Noninferiority Margin

The noninferiority margin was determined in consideration of the trade-off that would allow a higher safety outcome rate given the perceived benefit of a much better adherence to the regimen (and thereby assuring effectiveness) when IPT is initiated at pregnancy, specifically in programmatic settings. In the absence of any available statistical framework to guide quantification of the trade-off, clinician judgment was used with feedback from experts and external reviewers during study design.

Attribution of Relatedness for Primary Outcome

The main guidance for the attribution was that a decision of "at least possibly related" can be made if there is no alternative etiology that could explain the adverse event. Since the study is randomized and the endpoint review is blinded, any inflation of attribution to IPT (i.e. attribution of adverse event to placebo or to active INH when INH is not the true case) was ensured to be balanced and unbiased between the two arms.

Definition of Weight Loss and Adjudication for Primary Outcome

Unintentional weight loss is considered to be severe if there is 10% to 19% loss in body weight from baseline, and potentially life-threatening if there is at least 20% loss in body weight from baseline or aggressive intervention is indicated[22]; given that the criterion does not differentiate from weight loss that would be expected in postpartum period, the Independent Endpoint Review Committee was entrusted to consider this during adjudication of the primary safety outcome.

Handling of Censoring in Statistical Analyses

Participants who withdrew consent to complete the study or prematurely discontinued the study (except due to death) were censored at off study date and considered successes. A post-hoc sensitivity analysis that counted those lost to follow-up as failures was performed.

Figure S1. Time to Last Clinic Visit by Treatment Arm (Weeks from Randomization), Within Gestational Age Stratum

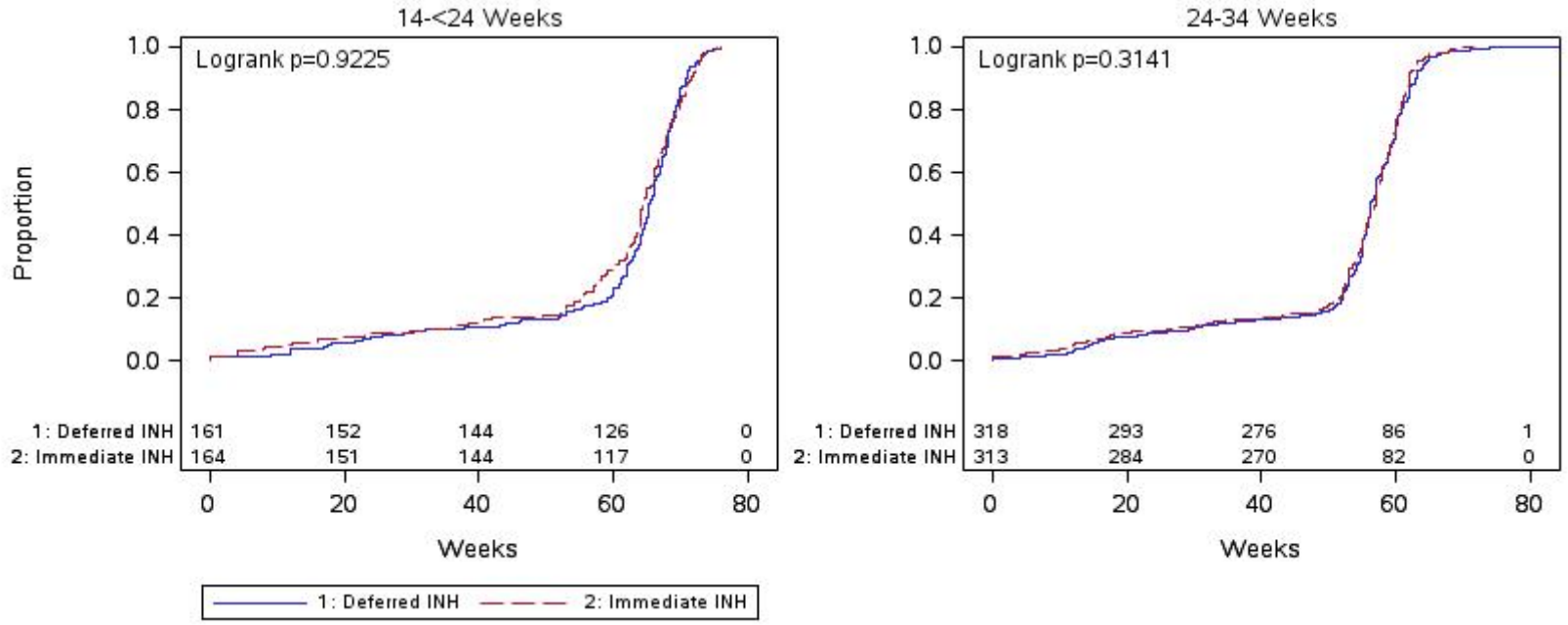


Figure S2a. Kaplan-Meier Plots of Time to Primary Safety Endpoint and Time to Secondary Maternal Safety Endpoint (Any Grade 3 or Higher Adverse Event) by Treatment Arm (Weeks from Randomization) and Gestational Age Stratum

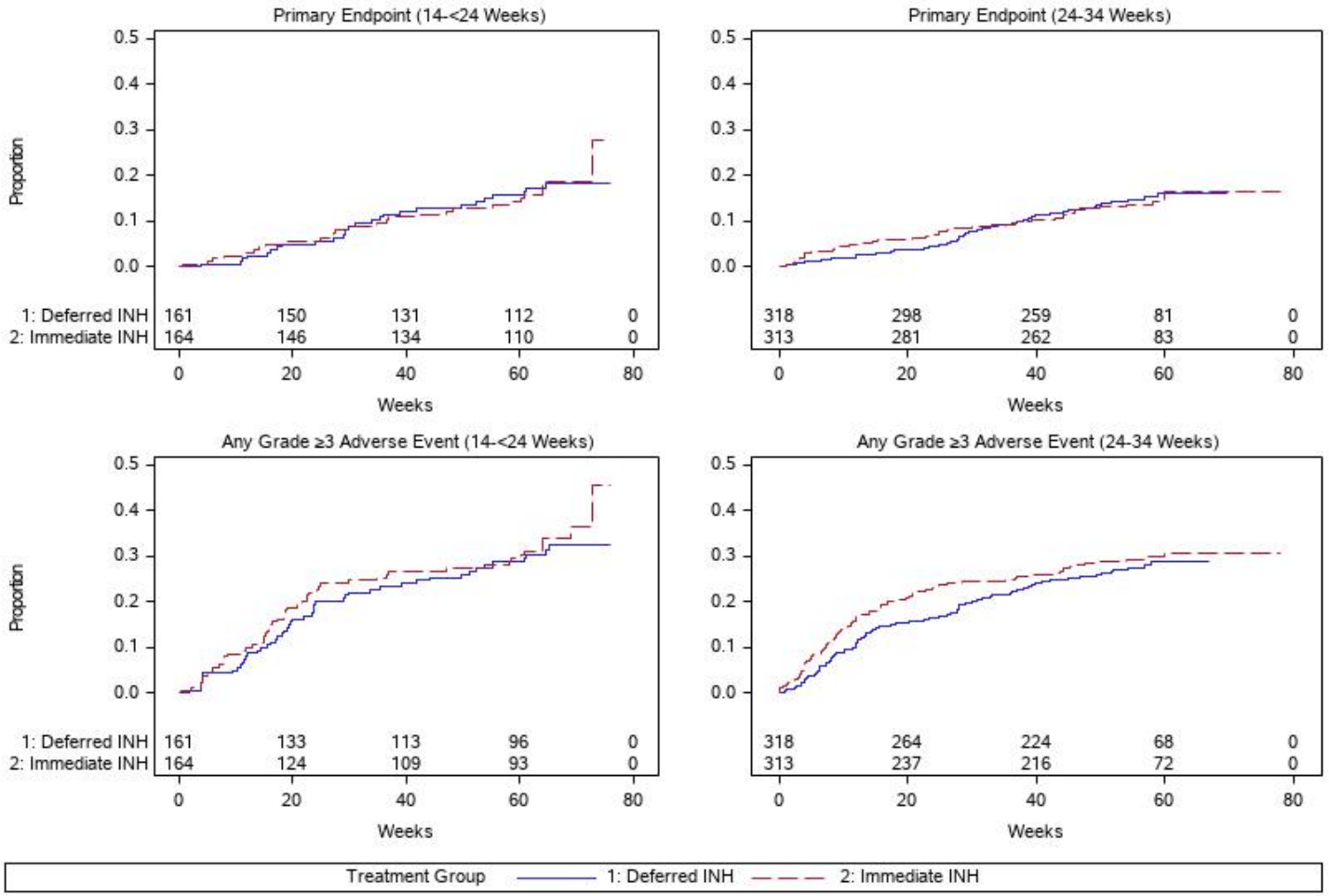


Figure S2b: Kaplan-Meier Plots of Time to Composite Maternal/Infant Efficacy Endpoint by Treatment Arm (Weeks from Randomization) and Gestational Age Stratum

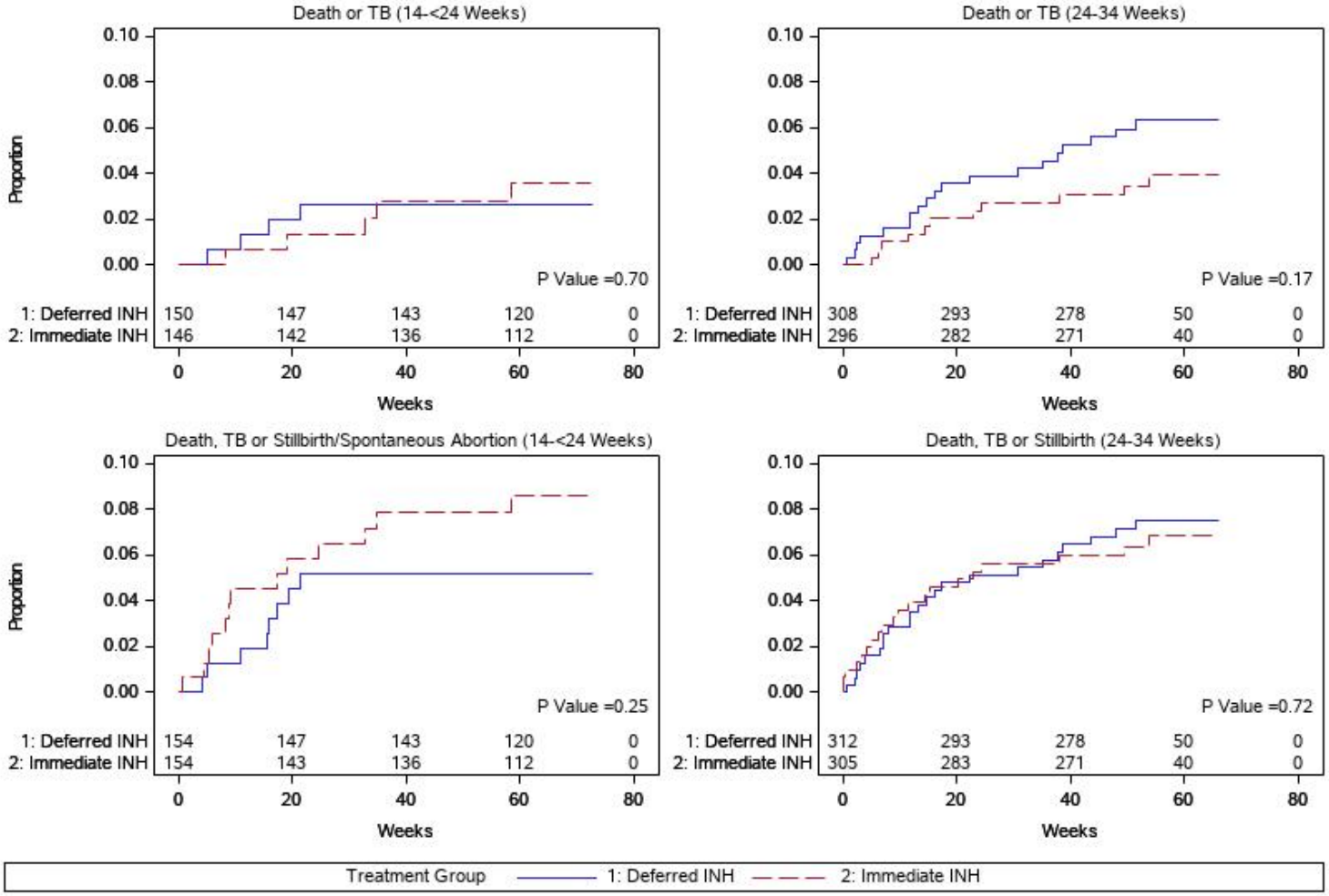
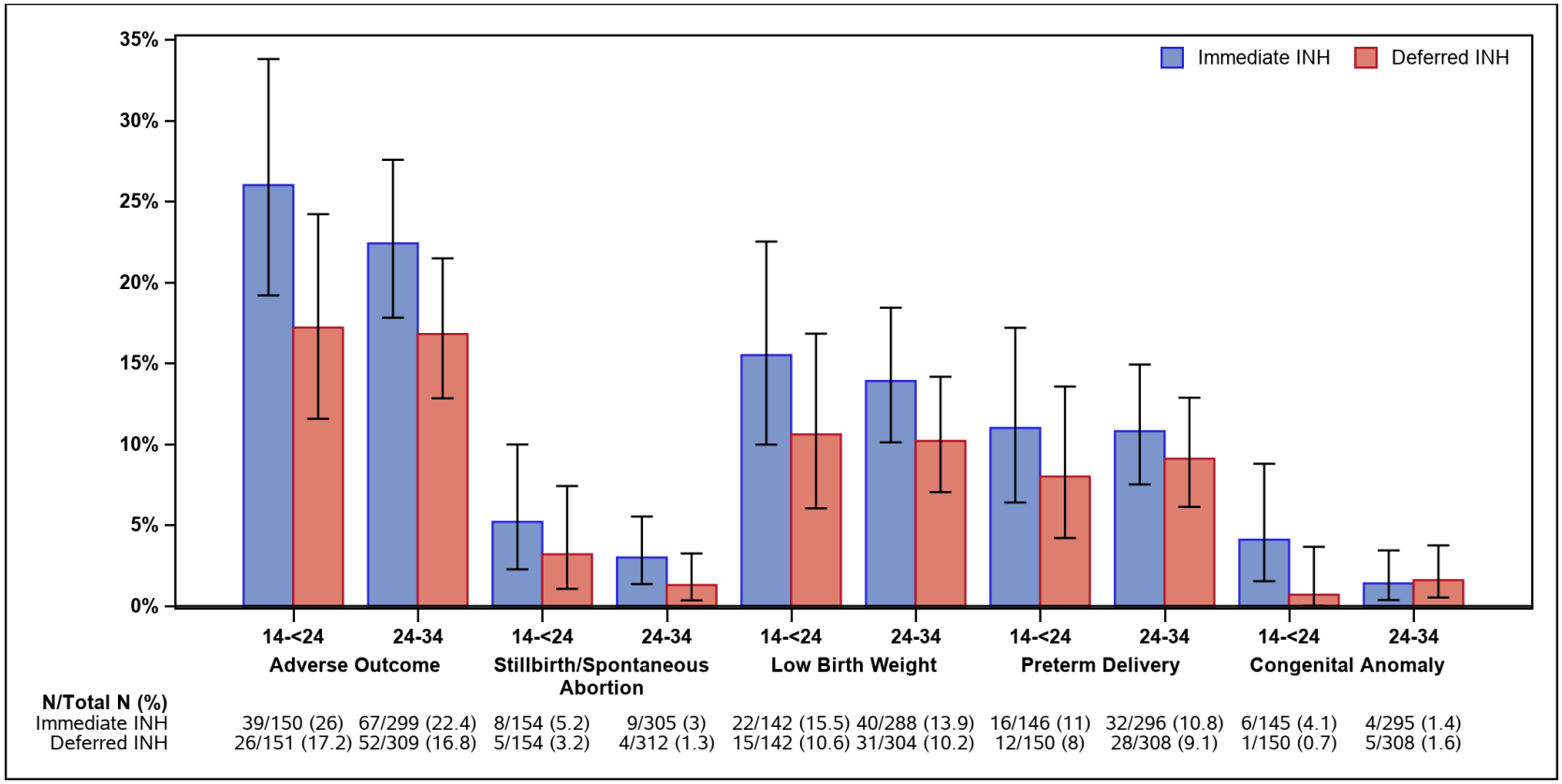


Figure S3. Post-Hoc Analysis of Adverse Pregnancy Outcomes by Treatment Arm and Gestational Age Stratum



N/Total N (%)	14-<24 Adverse Outcome	24-34 Adverse Outcome	14-<24 Stillbirth/Spontaneous Abortion	24-34 Stillbirth/Spontaneous Abortion	14-<24 Low Birth Weight	24-34 Low Birth Weight	14-<24 Preterm Delivery	24-34 Preterm Delivery	14-<24 Congenital Anomaly	24-34 Congenital Anomaly
Immediate INH	39/150 (26)	67/299 (22.4)	8/154 (5.2)	9/305 (3)	22/142 (15.5)	40/288 (13.9)	16/146 (11)	32/296 (10.8)	6/145 (4.1)	4/295 (1.4)
Deferred INH	26/151 (17.2)	52/309 (16.8)	5/154 (3.2)	4/312 (1.3)	15/142 (10.6)	31/304 (10.2)	12/150 (8)	28/308 (9.1)	1/150 (0.7)	5/308 (1.6)

This stratified gestational age analysis was post-hoc and not adjusted for multiple comparisons. Adverse pregnancy outcome was a composite of low birth weight (<2500 g), preterm delivery (<37 weeks of gestation according to the Ballard examination, when available, or obstetrical estimate), spontaneous abortion (<20 weeks of gestation), stillbirth (≥20 weeks of gestation), or major congenital anomaly (according to the Metropolitan Atlanta Congenital Defects Program of the US Centers for Disease Control and Prevention)[1].

Table S1. Analysis of Primary Safety Outcome[1] by Gestational Age and Per-Protocol

	Immediate INH		Deferred INH		
	n / Total n (%)	*IR/100 PY*	*n / Total n (%)*	*IR/100 PY*	*IRD (95% CI)*
Intention-to-treat population					
Primary safety outcome[2]					
14-<24 weeks GA	28/164 (17.1)	15.88	27/161 (16.8)	15.25	0.63 (-7.60, 8.86)
24-34 weeks GA	44/313 (14.1)	14.53	46/318 (14.5)	14.74	-0.20 (-6.25, 5.84)
Overall (weighted)	72/477 (15.1)	15.03	73/479 (15.2)	14.93	0.10 (-4.77, 4.98)
Per-protocol population					
Primary safety outcome[2]					
14-<24 weeks GA	24/128 (18.8)	16.21	25/128 (19.5)	16.88	-0.66 (-9.93, 8.60)
24-34 weeks GA	40/248 (16.1)	15.86	44/260 (16.9)	16.64	-0.78 (-7.73, 6.18)
Overall (weighted)	64/376 (17.0)	16.00	69/388 (17.8)	16.71	-0.71 (-6.27, 4.85)

[1] Noninferiority of immediate vs. deferred INH is concluded when the upper confidence limit of the 95% CI for the incidence rate (IR) difference (IRD) is less than the noninferiority margin of 5 per 100 person-years.

[2] The primary safety outcome is defined as the earlier of the two events: (1) Grade 3 or higher adverse event attributed to study treatment by an independent endpoint review committee, or (2) permanent discontinuation of study treatment due to toxicity.

Table S2a. Reasons for Study Treatment Discontinuation among Participants Who Permanently Discontinued Treatment Due to Toxicity

	Immediate INH	**Deferred INH**	**Overall**
	n (%)	*n (%)*	*n (%)*
Dizziness	1 (6%)	0 (0%)	1 (2%)
Eclampsia	0 (0%)	1 (4%)	1 (2%)
Fatigue	0 (0%)	1 (4%)	1 (2%)
Hepatotoxicity, asymptomatic	13 (81%)	16 (57%)	29 (66%)
Hepatotoxicity, symptomatic	1 (6%)	9 (32%)	10 (23%)
Peripheral neuropathy	1 (6%)	0 (0%)	1 (2%)
Weakness	0 (0%)	1 (4%)	1 (2%)
Total by treatment group	16	28	44

Table S2b. Maternal Off-Study Reasons

	Immediate INH *n (%)*	**Deferred INH** *n (%)*	**Overall** *n (%)*
Completed protocol	389 (82%)	396 (83%)	785 (82%)
Eligibility failure[1]	0 (0%)	1 (0%)	1 (0%)
Death	2 (0%)	4 (1%)	6 (1%)
Not able to get to clinic	21 (4%)	15 (3%)	36 (4%)
Withdrew consent prior to study completion	44 (9%)	34 (7%)	78 (8%)
Not willing to adhere to study requirements	2 (0%)	9 (2%)	11 (1%)
Site unable to contact participant	18 (4%)	20 (4%)	38 (4%)
Co-enrolled in another study	1 (0%)	0 (1%)	1 (0%)
Total by treatment group	477	479	956

[1]Diagnosed with confirmed MTB after enrollment

Table S3: Estimated Incidence Proportions[1] of Primary Safety Outcome and Key Secondary Maternal, Pregnancy, and Infant Outcomes by 48 Weeks Postpartum

Outcome	Immediate INH	Deferred INH	
	n / Total n (%)	*n / Total n (%)*	*% Diff (95% CI)*
Primary outcome[2]			
Intention-to-treat population	72/477 (15.1)	73/479 (15.2)	-0.2 (-4.7, 4.4)
Per-protocol population	64/376 (17.0)	69/388 (17.8)	-0.8 (-6.2, 4.6)
Secondary maternal outcomes			
Any grade 3 or 4 adverse event	144/477 (30.2)	136/479 (28.4)	1.8 (-4.0, 7.6)
Hepatotoxicity[3]	29/477 (6.1)	34/479 (7.1)	-1.0 (-4.2, 2.1)
Peripheral neuropathy	1/477 (0.2)	0/479 (0.0)	0.2 (-0.2, 0.6)
Death	2/477 (0.4)	4/479 (0.8)	-0.4 (-1.4, 0.6)
Death due to hepatitis while receiving INH[4]	1/477 (0.2)	1/479 (0.2)	0.0 (-0.6, 0.6)
Permanent discontinuation of trial regimen because of toxic effects	16/477 (3.4)	28/479 (5.8)	-2.5 (-5.1, 0.2)
Tuberculosis	3/477 (0.6)	3/478 (0.6)	0.0 (-1.0, 1.0)
Secondary pregnancy outcomes			
Adverse pregnancy outcome[5]	106/449 (23.6)	78/460 (17.0)	6.7 (0.8, 11.9)
Stillbirth/spontaneous abortion	17/459 (3.7)	9/466 (1.9)	1.8 (-0.4, 4.1)
Low birth weight	62/430 (14.4)	46/446 (10.3)	4.1 (-0.3, 8.6)
Preterm delivery	48/442 (10.9)	40/458 (8.7)	2.1 (-1.8, 6.1)
Congenital anomaly	10/440 (2.3)	6/458 (1.3)	1 (-0.9, 3.0)
Secondary infant outcomes			
Any grade 3 or 4 adverse event	191/445 (42.9)	192/464 (41.4)	1.6 (-4.9, 8.0)
HIV infection	3/439 (0.7)	7/458 (1.5)	-0.9 (-2.2, 0.5)
Infant death: 0-48 weeks after birth	11/445 (2.5)	17/464 (3.7)	-1.2 (-3.4, 1.0)
Neonatal death: 0-7 days after birth	4/445 (0.9)	5/464 (1.1)	-0.2 (-1.5, 1.1)
Tuberculosis	0/445 (0.0)	1/464 (0.2)	0.0 (-0.8, 0.9)

[1]All analyses are intent-to-treat unless otherwise specified
[2]The primary safety outcome is defined as the earlier of the two events: (1) Grade 3 or higher adverse event attributed to study treatment by an independent endpoint review committee, or (2) permanent discontinuation of study treatment due to toxicity.
[3] Hepatotoxicity was defined as Grade 3 or higher liver function tests; total bilirubin ≥ Grade 2 and ALT ≥ Grade 2; or ALT ≥ Grade 2 with symptomatic clinical hepatitis.
[4] Post-hoc analysis
[5] Adverse pregnancy outcome was a composite of low birth weight (<2500 g), preterm delivery (<37 weeks of gestation according to the Ballard examination, when available, or obstetrical estimate), spontaneous abortion (<20 weeks of gestation), stillbirth (≥20 weeks of gestation), or major congenital anomaly (according to the Metropolitan Atlanta Congenital Defects Program of the US Centers for Disease Control and Prevention)[24].

Table S4. Post-hoc Sensitivity Analyses of Primary Outcome

Analysis	Immediate INH		Deferred INH		
	n / Total n (%)	*IR/100 PY*	*n / Total n (%)*	*IR/100 PY*	*IRD (95% CI)*
Worst-case[1]	149/477 (31.2)	31.11	145/479 (30.3)	29.65	1.45 (-5.49, 8.4)
Complete-case	72/399 (18.0)	17.14	73/406 (18.0)	16.94	0.21 (-5.34, 5.75)

[1]Participants who discontinued study prematurely were counted as failures

A substantial proportion of participants prematurely discontinued the study. In large part this was due to the patient safety letter that was issued in February 2016 (at the recommendation of the DSMB) about potential risks of IPT and ART after 2 deaths from fulminant liver failure occurred in the study. To address the missing data, our primary analysis censored data of participants at their times of premature study discontinuation. This is generally a reasonable approach to handling missing data for this type of outcome. The primary MAR-like assumption for such an analysis is non-informative independent censoring which is the most realistic in a confirmatory clinical trials setting. Further post-hoc comparison did not show significant between arm differences in incidence of premature study follow-up.

To assess the robustness of the primary analysis results to other assumptions, we performed straightforward post hoc sensitivity analyses that counted those who were discontinued the study prematurely as failures (worst-case analysis) and another sensitivity analysis that included only those in the intent to treat population who completed their planned study follow-up (complete-case analysis). For the worst-case analysis, the estimated primary outcome incidence rate was 31.11 per 100 PY in the immediate INH arm and 29.65 per 100 PY in the deferred INH arm, with an IRD = 1.45 and 95% CI: -5.49 to 8.4. For the complete-case analysis, which is unbiased if the complete cases represent a random sample of the study population (MCAR), the estimated primary outcome incidence rate was 17.14 per 100 PY in the immediate INH arm and 16.94 per 100 PY in the deferred INH arm, with an IRD = 0.21 and 95% CI: -5.34 to 5.75; despite the upper limit of the 95% CI being close to the margin, it is not less than 5 and we cannot conclude non-inferiority of the immediate INH arm with this analysis.

Table S5. Maternal Deaths

Characteristic	Study Arm					
	Immediate	Immediate	Deferred	Deferred	Deferred	Deferred
	Participant 1	Participant 2	Participant 3	Participant 4	Participant 5	Participant 6
Age (years) at entry	34	38	27	36	25	33
CD4 count (cells/mm^3) at labor/delivery	459	469	402	609	431	533
CD4 count (cells/mm^3) at screening	351	426	333	591	188	642
HIV RNA (copies/mL) at entry	312	<40	<40	<40	159	<40
BMI at entry	24.0	20.9	29.0	23.0	39.6	21.1
Hepatitis B status at entry	Negative	Negative	Negative	Negative	Negative	Negative
Hepatitis C status at entry	Negative	Negative	Unknown	Negative	Negative	Negative
GA at entry (weeks)	33	21	31	26	26	30
Postpartum (PP) week at death	12 weeks	39 weeks	5 weeks	18 weeks	8 weeks	6 weeks
Time on INH	13 weeks (4 AP, 9 PP)	27 weeks (19 AP, 8 PP)	Never started	1 week PP	Never started	Never started
ART regimen initiated	TDF/3TC/EFV	TDF/FTC/EFV	TDF/3TC/EFV	TDF/3TC/EFV	TDF/3TC/EFV	TDF/3TC/EFV

	Started 1 week prior to entry	Started 2.4 years prior to entry	Started 4 months prior to entry	Started 2 months prior to entry	Started 3 weeks before entry	Started 1 month before entry
Concomitant medication	No	Cotrimoxazole	Cotrimoxazole	Cotrimoxazole	Cotrimoxazole & Herbal*	Cotrimoxazole
Active alcohol use*	No	No	No	No	No	No
Death cause	Fulminant hepatitis	Bacterial sepsis	Fulminant hepatitis	Fulminant hepatitis	Hepatitis	Pneumonia
Attribution to study drug	Related	Not related	Not related	Related	Not related	Not related

AP: antepartum; PP: postpartum; TDF: tenofovir; 3TC: lamuvidine; FTC: emtricitabine; EFV: efavirenz; *based on Expedited Adverse Event report narrative

Brief narratives of the 4 liver-related deaths based on AE reports

Of the four women who died from liver-related causes, two never received active INH. The first woman who never received INH was a 27 year old woman. She entered the study at 31 weeks gestation with a BMI of 29, a CD4 of 333 and an HIV RNA of <40 copies/ml and she had been on ART TDF/3TC/EFV along with cotrimoxazole for 4 months prior to study entry. She was randomized to the deferred INH arm. At entry, she had a Grade 1 ALT and was HBV negative and HCV unknown. Because of the grade 1 ALT, the site repeated the LFTs 2 days after entry and observed a grade 2 ALT, a grade 3 AST and normal bilirubin and she remained asymptomatic. She returned to the clinic 6 days later and reported no symptoms but she now had a grade 4 AST and ALT and had her study drug (placebo) was held and then discontinued permanently after this was confirmed a few days later. Her LFTs normalized. She had a normal vaginal delivery at 37 weeks gestation and remained on her ART. However, at postpartum week 3 she developed jaundice and she was briefly hospitalized a few days later. Her treating clinician switched her efavirenz to lopinavir/ritonavir. She had worsening liver dysfunction and died of fulminant hepatitis. No hepatitis A, herbal or acetaminophen use was reported. This death was not INH-related.

The second woman who never started INH but had a liver-related death was a 25 year old woman. At 26 weeks gestation, she was randomized to the deferred INH arm and started on placebo. At entry, she had a BMI of 39.6, a CD4 of 188, and a HIV RNA of 159 copies/ml. She was HBV and HCV negative and had no alcohol use. She was on efavirenz-based ART along with cotrimoxazole that was started 3 weeks prior to study entry. She had a normal vaginal delivery at 41 weeks; she had a grade 1 ALT at delivery and then 4 days after delivery developed a grade 3 AST without any symptoms. She left the study site to be at her native home for postpartum

care and was not readily contactable. She was traced with extensive site follow-up and 4 weeks after delivery her mother called the study team back and reported participant was having vomiting and yellow eyes. She stopped study drug (blinded placebo) and she had some improvement but then was hospitalized 3 weeks later and had sudden worsening of symptoms and liver enzymes and died. She was reportedly also on an herbal treatment of unknown type or duration and remained on efavirenz and cotrimoxazole until she was hospitalized per outside available records and verbal autopsy. No hepatitis A or acetaminophen use was reported. This death was also not INH-related.

The other two liver-related deaths were deemed to be INH-related.

The first was a 34 year old woman. She was randomized to the immediate INH arm. At study entry, she was 33 weeks pregnant with a BMI of 24. She was HBV and HCV negative, alcohol negative, had normal LFTs, and her CD4 was 351 with a HIV RNA of 312 copies/ml. Her EFV-based ART was started 1 week prior to study entry. At 39 weeks gestation, she had a normal vaginal delivery but was noted to have a grade 4 neutropenia so study drug (INH) was held. Her neutropenia resolved and at 2 weeks postpartum she restarted her INH. One week after resuming she was observed to have a grade 1 ALT, AST and was asymptomatic. Over the subsequent 4 weeks she developed gastritis symptoms but her LFTs remained grade 1 and she was given some antacids. At 4 weeks postpartum, she developed vomiting, decreased appetite and on the same day her study drug (INH) was stopped. Unfortunately, post-cessation of her study drug INH, she developed worsening symptoms of clinical hepatitis and advanced to grade 4 AST and ALT and died in the hospital. No hepatitis A, herbal or acetaminophen use was reported.

The second women who initiated INH in the study and died was a 36 year old woman. She enrolled at 26 weeks gestation with a BMI of 23. Her CD4 was 591 cells/mm^3 and her HIV RNA was <40 copies/ml on an EFV-based ART regimen along with cotrimoxazole. She was randomized to the deferred INH arm. At week 12 postpartum she started INH and received one week of INH. She was noted to have a grade 2 ALT and was asymptomatic. The study clinician held her study drug (active INH). Over the next 5 weeks monitoring of LFTs continued after study drug discontinuation as per protocol SOE with no missed sessions but, unfortunately, her LFTs continued to worsen and the woman became symptomatic and eventually died. No hepatitis A, herbal or acetaminophen use was reported.

Table S6. Maternal Active Tuberculosis Cases

Participant	Treatment group	Study week of onset	Week of onset relative to delivery	Type of MTB	DST profile	Age at entry	CD4 at entry	IGRA status at entry	TST status at delivery	IGRA status prior to TB diagnosis	TB exposure
1	Immediate INH	55	48PP	Confirmed pulmonary MTB	INH-resistant	27	254	Positive	Positive	Positive	No
2	Immediate INH	38	28PP	Confirmed pulmonary MTB	INH-sensitive	25	289	Negative	Positive	Positive	No
3	Immediate INH	33	10PP	Probable pulmonary MTB	N/A	29	678	Positive	Positive	Positive	No
4	Deferred INH	35	27PP	Probable pulmonary MTB	N/A	40	261	Negative	Negative	Negative	No
5	Deferred INH	51	40PP	Confirmed pulmonary MTB	INH-sensitive	31	79	Indeterminate	Negative	Indeterminate	No
6	Deferred INH	48	36PP	Confirmed pulmonary MTB	INH-sensitive	32	504	Positive	Negative	Positive	No

Table S7. Grade 3 and 4 Liver Enzyme Abnormalities and Deaths Due to Liver Failure in 7 Recent International Trials of Isoniazid (INH) Preventive Therapy (IPT)

Author/Journal	Sites	Arms/HIV	ART+IPT	LFT monitoring	Grade 3 or 4 LFTs in INH arm	Deaths due to hepatic failure in INH arm
Swindells et al NEJM 2019 BRIEF TB[2]	Multicountry Sub Saharan Africa, South Africa, Asia, Haiti, US	1HP vs. 9 mo of IPT HIV+: All enrolled, N=3000	Yes, 755/1498 (50%)	Baseline and only if symptomatic	42/1498 (2.8%)	0 of 1498 (0%)
Menzies NEJM 2018[3]	Australia, Benin, Brazil, Canada, Ghana, Guinea, Indonesia, Saudi Arabia, South Korea	4 mo Rifampin vs. 9 mo of IPT Total enrolled n=6012 HIV+ N=242	Yes, 123 HIV+ in IPT arm	Baseline and 1 month	65/3205 (2%) HIV-specific data not reported	1 death of 3205 (0.03%) Death judged possibly related to study by two panel members and unlikely related by one Unknown if HIV+
ANRS TEMPRANO NEJM 2015[4]	Ivory Coast	4 arms Early ART, Early ART+IPT; Deferred ART; Deferred ART+IPT HIV+, All enrolled, n=2056	Yes, 2 arms n=1030	Baseline and every 6 months	12/1030 (1.1%)	2 hepatitis deaths reported but unclear which arms and whether drug related

Author/Journal	Sites	Arms/HIV	ART+IPT	LFT monitoring	Grade 3 or 4 LFTs in INH arm	Deaths due to hepatic failure in INH arm
Rangaka et al Lancet 2014[5]	South Africa	ART vs. ART+ 12 months of IPT HIV+, All enrolled, n=1329	Yes, n=662 in 12 months of IPT arm	Baseline, monthly x3 months then q3months	19/662 (2.9%)	16 deaths in INH arm (0.9/100PY); 2 TB deaths, 6 non TB and nonstudy drug, 8 unknown with 2 occurring during IPT. Relatedness not determined.
Sterling et al NEJM 2011,[6] AIDS 2016[7]	US, Brazil, Spain, Peru, Canada, Hing Kong	Weekly isoniazid +rifapentine vs. 9 mo. IPT HIV+ 193 of 7731 enrolled	Yes, n=58 of 193 HIV+ on ART in 9 months IPT arm		2.7% in whole trial in 9H arm, 8/186 (4%) discontinued 9H due to hepatotoxicity in HIV study. LFT monitoring only done at baseline	1 death due to chronic liver disease or cirrhosis on INH or within 60 days of last dose
Martinson et al NEJM 2011[8]	South Africa	4 arms Isoniazid+rifpentine for 12 weeks vs. isoniazid+rifampin for 12 weeks vs. IPT continuous up to 6 years vs. 6 mo IPT HIV+ all n=1148	327 in IPT arm None at entry, 18.9% started ART during study	Baseline, 1,2,6 months	17/327 (5.2%) Grade 3 14/327 (4.3%) Grade 4	0/25 deaths due to study drug
Samandari et al Lancet 2011 BOTUSA[9]	Botswana	6months of IPT vs. 36 months of IPT HIV+ all n=1995	Yes, n=946/1995 started ART during the study	Baseline, before ART started and if clinically indicated	29 of 1995 (1.45 per 100 PY biochemical hepatitis); 8 had clinical hepatitis (0.4/100PY), 2	1 died of hepatic encephalopathy

Author/Journal	Sites	Arms/HIV	ART+IPT	LFT monitoring	Grade 3 or 4 LFTs in INH arm	Deaths due to hepatic failure in INH arm
			6months IPT vs. 36 months of IPT (Total enrolled n=1995)		hepatic encephalopathy (0.1/100PY)	

Abbreviations: ART: Antiretroviral therapy; INH: Isoniazid; IPT Isoniazid Preventive Therapy

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