CROI 2018 PRESS CONFERENCE ABSTRACTS: Wednesday, March 7, 2018
Abstracts # 135, 137, 141, 142LB, 128, 129, 130 embargoed until Wednesday, March 7, 2018 at 12:00 pm ET
Abstract #81LB embargoed until Tuesday, March 6, 2018 at 12:00 pm ET
Abstract #166 embargoed until Wednesday, March 7, 2018, 1:15 pm ET

Abstract Number 142LB - (Oral)

RANDOMIZED TRIAL OF SAFETY OF ISONIAZID PREVENTIVE THERAPY DURING OR AFTER PREGNANCY

Clinical: (O) Tuberculosis and Other Opportunistic Infections

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Background: The safety, efficacy, and optimal timing of isoniazid preventive therapy (IPT) for HIV-positive pregnant women on antiretroviral therapy (ART) is unknown. We hypothesized that IPT can be safely initiated during pregnancy.

Methods: A Phase IV randomized, double-blind, placebo-controlled trial compared initiation of 28 weeks of IPT in antepartum (AP; immediate) (arm A) versus at 12 weeks postpartum (PP; deferred) (arm B) in HIV-positive women from TB-endemic areas in Africa, Asia, and Haiti. Randomization 1:1 was stratified by gestational age [GA] (14-<24 weeks, 24-34 weeks); mother-infant pairs were followed to week 48 PP, with safety evaluations performed every 4 weeks. The primary safety endpoint was treatment-related maternal adverse events (AE) ≥ grade 3 or permanent drug discontinuation due to toxicity. The non-inferiority margin (NIM) was an incidence rate (IR) of 5/100 person-years (PY), assuming a 5/100 PY IR in arm B based on reports in non-pregnant HIV-positive adults. Secondary outcomes were maternal hepatotoxicity, maternal/infant death, TB, adverse pregnancy outcomes, infant AE.

Results: Among 956 enrolled, 93% were black, median age was 29 years, median CD4 was 493 cells/μL, 30% were IGRA+, 955 (>99%) were on ART (85% efavirenz-based), 63% had undetectable HIV-1 RNA, and 34% were 14-<24 weeks GA. Median follow-up was 58.6 weeks. 147 (15%) reached the primary outcome (74 in arm A, 73 in arm B), with IRs 15.4 and 14.9/100 PY, respectively (IR difference=0.5/100 PY, [95%CI: -4.4, 5.4]; Table).171 women discontinued the study prematurely; 6 died (2 in arm A, 4 in arm B), with 3 deaths due to treatment-related hepatotoxicity (1 in arm A, 2 in arm B) and one non-treatment-related hepatotoxicity in arm B; 77 withdrew consent (most after DSMB and sponsor-required safety memo about risk of death from IPT); 75 were lost to follow-up. There were no statistical differences in IRs of any maternal grade ≥3 AE, all-cause hepatotoxicity, or infant grade ≥3 AE between arms. There was no difference in maternal TB or infant TB by study arm. Adverse pregnancy outcomes however were significantly higher in arm A vs. B (23% vs 17%; p=0.009).

Conclusion: IR for the primary safety outcome was higher than expected and similar for immediate vs. deferred IPT, but did not meet the pre-specified NIM. TB incidence was low. Of note, immediate IPT was associated with excess adverse pregnancy outcomes. The recommendation to initiate IPT during pregnancy in HIV-positive women on ART needs re-evaluation.