High programmatic isoniazid preventive therapy (IPT) use in pregnancy among HIV-infected women

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Abstract

\textbf{Background:} WHO recommends isoniazid preventive therapy (IPT) for people living with HIV (PLHIV) to prevent TB, including pregnant women. Recent trial results suggest increased adverse pregnancy outcomes associated with IPT during pregnancy. Data are limited regarding programmatic IPT use in pregnant PLHIV.

\textbf{Methods:} We assessed previous programmatic IPT during pregnancy among HIV-infected mothers on enrolment to an infant TB prevention trial in Kenya. Pregnancy IPT use was assessed by estimated conception date assuming 38 weeks gestation. Correlates of initiation and completion were analyzed by relative risk regression, using generalized linear models with log link and Poisson family adjusted for IPT initiation year.

\textbf{Results:} Between August 15, 2016 to June 6, 2018, 300 HIV-infected women enrolled at 6 weeks postpartum. Two-hundred twenty-four (74.7\%) women reported previous IPT, of whom
155/224 (69.2%) had any pregnancy IPT use. Forty-five (29.0%) initiated pre-conception extending into early pregnancy, 41 (26.5%) initiated and completed during pregnancy, and 69 (44.5%) initiated in pregnancy and extended into early postpartum. Median gestational age at IPT pregnancy initiation was 15.1 weeks (IQR 8.3–28.4). Pregnancy/early postpartum IPT initiation was associated with new pregnancy HIV diagnosis (aRR 1.9 95%CI 1.6–2.2, p<0.001). Six-month IPT completion rates were high (147/160 [91.9%]) among women with sufficient time to complete prior to trial enrolment, and similar among pre-conception or during pregnancy initiators (aRR 0.93 [95%CI 0.83–1.04, p=0.19]).

Conclusions: Programmatic IPT use was high in pregnant PLHIV, with frequent periconception and early pregnancy initiation. Programmatic surveillance could provide further insights on pregnancy IPT implementation and maternal and infant safety outcomes.

Keywords
tuberculosis; HIV; periconception; pregnancy; isoniazid; tuberculosis preventive

Introduction

The World Health Organization (WHO) recommends isoniazid preventive therapy (IPT) to prevent tuberculosis (TB) for people living with HIV (PLHIV), including pregnant women [1]. Kenya endorsed routine IPT in 2014 national guidelines [2], with ensuing rapid expansion in HIV care programs [3, 4]. Neither Kenyan nor WHO guidelines specify whether IPT provision should preferentially occur during pregnancy or postpartum [1, 3, 4]. Pregnancy is a key time for HIV care engagement and provides an operationally strategic time for TB prevention. TB during pregnancy is associated with poor maternal and infant outcomes [5–7], even with antiretroviral therapy (ART) and TB treatment [8]. ART and IPT adherence may be higher during pregnancy than postpartum [9–13]. Pregnancy IPT safety concerns stemmed initially from US-based hepatotoxicity reports in retrospective cohorts and isoniazid-related death case series [14, 15]. In subsequent secondary analyses of randomized trials, TB preventive therapy did not appear associated with adverse pregnancy outcomes or hepatotoxicity [16–18]. IPT implementation was feasible in a Lesotho observational study of pregnant PLHIV primarily on AZT prophylaxis, though with suboptimal completion rates [11]. However, in the first trial designed specifically to study IPT safety in pregnant and postpartum women living with HIV (WLHIV) on ART (TB APPRISE), women randomized to IPT during pregnancy had increased adverse pregnancy outcomes, compared to women randomized to postpartum IPT [19].

Data are limited regarding programmatic IPT provision in pregnant WLHIV, including periconception and early pregnancy, in the era of widespread ART availability and increasing IPT implementation [20]. We estimated timing, prevalence, and correlates of maternal programmatic IPT use during pregnancy, among WLHIV on enrolment into an infant TB prevention trial in western Kenya.
Methods

In the ongoing parent trial, HIV-exposed infants are enrolled at 6–10 weeks of age from HIV prevention of mother-to-child transmission (PMTCT) clinics in western Kenya and randomized to 12 months isoniazid or no isoniazid with a primary endpoint of \textit{M. tuberculosis} infection (\textcircled{1}). Premature (<37 weeks gestation) or low birthweight (<2.5 kg) infants, and mothers with TB disease in past year, are ineligible. On enrollment, sociodemographic, pregnancy, TB history, and previous IPT (including timing of initiation and duration) data by maternal report were collected using structured questionnaires. Date of HIV diagnosis and ART start date were abstracted from clinical charts. Delivery date was confirmed from infant health passbooks. Currently, Kenyan and WHO guidelines do not specifically recommend IPT for HIV-exposed infants without known TB contact, despite their potentially increased risk of TB. Maternal IPT was not provided within the infant trial but is considered a part of routine HIV care in Kenya and did not affect trial eligibility. Per Kenyan and WHO guidelines, all PLHIV should be screened at routine HIV care visits using symptom-based TB screening and those with negative symptom screening are to be evaluated for IPT [1, 3, 4].

For this study, pregnancy IPT use was assessed using IPT initiation date and estimated date of conception, assuming 38 week (266 day) gestation preceding infant birthdate [18, 21]. IPT initiation was considered pre-conception if >266 days before delivery, during pregnancy if 0 to 266 days before delivery, or postpartum if after delivery. Correlates of initiation and completion were analyzed using a relative risk (RR) regression generalized linear model (GLM) with log link and Poisson family adjusted for year of IPT initiation. Sensitivity analyses were performed assuming 35–41 weeks gestation to account for gestational length variability.

Data were entered into Research Electronic Data Capture (REDCap, Vanderbilt University, Nashville, Tennessee, USA) and analyzed with STATA version 15 (StataCorp, College Station, Texas, USA).

Ethics Approval

Written informed consent was obtained from mothers. Parent trial procedures were approved by University of Washington and Kenyatta National Hospital/University of Nairobi ethical review boards, and Kenya Pharmacy and Poisons Board.

Results

Between August 15, 2016 to June 6, 2018, 300 WLHIV were enrolled at median of 6.3 (IQR 6.0–6.6) weeks postpartum. Median maternal age and CD4 were 27 years (IQR 24–31) and 478 cells/mm$^3$ (IQR 330–673), respectively (Supplemental Table). All were on ART, with 219 (73.0%) starting ART prior to pregnancy at median of 2.4 years (IQR 1.3–5.1) prior to estimated conception. The most common ART regimens were efavirenz- (with tenofovir and lamivudine (68.7%)), and nevirapine-based (with tenofovir and lamivudine (13.0%) or zidovudine and lamivudine (6.3%)). Thirty-two (10.7%) reported history of TB.
Pregnancy IPT exposure and timing.

Women initiated IPT between February 2014 through March 2018. Two-hundred twenty-four (74.7%) women reported previous IPT, of whom 95 (42.4%) were estimated to have initiated pre-pregnancy, 110 (49.1%) during pregnancy, and 19 (8.5%) postpartum (Figure 1). Median estimated gestational age at pregnancy initiation was 15.1 weeks (IQR 8.3–28.4) with 51 (46.4%) women starting in first, 30 (27.3%) in second, and 29 (26.4%) in third trimester (Table 1). Including periconception initiation, 155 (69.2%) had any pregnancy IPT use: 45 (29.0%) started pre-conception and completed during pregnancy, 41 (26.5%) initiated and completed during pregnancy, and 69 (44.5%) initiated in pregnancy and extended postpartum (Supplemental Figure). Of 63 women on IPT at early postpartum enrollment, 44 (69.8%) started during pregnancy, while 19 (30.2%) initiated postpartum at median 2.5 weeks (IQR 1.3–5.9) after delivery. Pregnancy/early postpartum rather than preconception IPT initiation, was associated with new HIV diagnosis during pregnancy (aRR 1.9 [95%CI 1.6–2.2, p<0.001]) and younger age (aRR 0.97 per year [95%CI 0.95–0.99, p=0.002]) (Supplemental Table). In sensitivity analyses, assuming 35–41 week gestation, 45.5–51.8% of women would have initiated IPT during pregnancy.

Timing of ART and IPT initiation.

ART initiation occurred between October 2005 through April 2018. Of 223 women with available ART and IPT initiation dates, 190 (85.2%) started IPT at a median of 1.9 years (IQR 0.5–4.3) after ART, 8 (3.6%) started same day, and 25 (11.2%) started IPT before ART. More than half of women with a known pre-pregnancy HIV diagnosis also initiated IPT pre-conception (95/171, 55.6%); an additional 69/171 (40.5%) with pre-pregnancy HIV diagnosis initiated IPT later during pregnancy.

IPT completion.

Most women with an adequate window of time prior to study enrollment, reported completing a 6-month IPT course (147/160 [91.9%]). The remaining (8.1%) reported a median of 3 months of IPT (IQR 2–3). Of 63 currently on IPT, 15 (23.8%) were in their 6th month of IPT at early postpartum enrollment. Completion rates were similar among pregnancy vs. pre-conception initiators (aRR 0.93 [95%CI 0.83–1.04, p= 0.19]) (Supplemental Table).

Repeat IPT initiation.

Eleven (10%) women with IPT pregnancy initiation reported an additional prior course, including 7 who previously completed a full 6-months.

Discussion

In this study, nearly 70% of early postpartum WLIV were estimated to have IPT use during pregnancy, with frequent periconception and early pregnancy initiation. IPT initiation during pregnancy was associated with HIV diagnosis during pregnancy. Six-month completion rates were high (91.9%) and similar between women initiating during non-pregnant and pregnancy periods.
In countries such as Kenya, which are widely implementing IPT, antenatal care appears to be a key opportunity for IPT initiation particularly among WLHIV newly diagnosed with HIV. Although WHO and Kenya current IPT recommendations include pregnant women [22], and IPT in pregnant WLHIV appears cost-effective [23, 24], until recently rigorous safety evidence has been lacking. In secondary analyses of the Botswana-based BOTUSA trial (6 vs. 36 months IPT), long-term IPT and ART were not associated with adverse pregnancy outcomes, and no severe isoniazid-associated adverse events including hepatitis were observed [16]. In the recently completed TB APPRISE trial of IPT safety in pregnant and postpartum WLHIV, there were no significant differences in overall maternal adverse events between antenatal vs. postpartum IPT [19]. However, postpartum hepatotoxicity rates were higher than expected irrespective of IPT timing, and IPT during pregnancy was associated with increased risk of composite adverse pregnancy outcomes with trend towards association with earlier pregnancy initiation [19]. IMPAACT-sponsored Study 2001 phase I/II trial is investigating safety and pharmacokinetics of once-weekly isoniazid and rifapentine (3HP) [25], and efforts are under development to evaluate safety of one-month daily isoniazid and rifapentine (1HP) in pregnant and postpartum WLHIV.

Importantly in our study, there were high rates of periconception and early pregnancy (median 15 weeks gestation) IPT initiation among women who may not have yet known they were pregnant. Recent reports of neural tube defects potentially associated with periconception dolutegravir after Botswana’s national roll-out underscore need for strong surveillance systems [26]. The U.S. Task Force on Research Specific to Pregnant and Lactating Women (PRGLAC) identified major gaps in data availability regarding medication safety in pregnancy and lactation [27], and recent publications have argued for inclusion of pregnant women in TB treatment and prevention trials [28, 29]. By enrolling healthy infants into the parent study, we cannot evaluate maternal IPT and pregnancy or infant birth outcomes. However, using standardized methods to estimate gestational age we were able to estimate high rates of periconceptional and pregnancy IPT use.

We noted examples of potentially inadvertent repeat provision of IPT to women during pregnancy, highlighting need for HIV and PMTCT care coordination. Completion rates were higher than previously reported for low and middle income countries in a systematic review of latent TB treatment cascade of care (52%) [30], and specifically among pregnant WLHIV in Lesotho (65%) [11] and South Africa (32%) [13], and in ongoing efforts to integrate TB-HIV, reproductive, and peripartum services in Swaziland (49%) [31]. Uptake was comparatively high in Swaziland family planning services (60%) (compared to antenatal [35%], and postnatal care [22%]) identifying opportunities for TB prevention for WLHIV of reproductive potential [31]. Maternal motivation to take ART and IPT appears to differ throughout the peripartum period, and is likely an important factor in successful implementation [12, 13].

Our study has limitations including reliance on maternal report of IPT initiation date and duration of therapy, which may have affected our estimates of IPT use and completion. Because our data was a retrospective review of programmatic maternal IPT use, adherence monitoring was not performed. Data regarding self-report of programmatic IPT adherence in pregnant and postpartum women are limited. Among 24 women receiving postpartum IPT
enrolled in a South African study of maternal priorities for preventive therapy, short term adherence by urine testing was lower than maternal report (67% vs. 96%); adherence during pregnancy was not measured [13]. This suggests self-report data may over-estimate adherence. In the TB APPRISE trial, adherence was measured via self-report and pill count, but data are not yet currently available. Pregnancy period estimation assuming 38 weeks gestation could have led to misclassification of IPT timing during periconception and early pregnancy. Moro et al. used similar methods to estimate TB preventive therapy pregnancy exposure in PREVENT TB and iAdhere trials [18]. To address this limitation, we performed sensitivity analyses assuming variable gestation length. Women in our study were enrolled in an infant TB prevention trial with exclusion criteria of prematurity and low birth weight; therefore, we are unable to assess pregnancy and birth outcomes. Women with previous isoniazid-related adverse events may have been less likely to participate in an infant IPT trial. Participants in the parent trial may not reflect all WLHIV in routine peripartum care at the sites, affecting generalizability.

In summary, we describe high programmatic IPT use during pregnancy among HIV-infected women including periconception and early gestational stages, and high completion rates. In light of recent trial results, surveillance within programmatic IPT use among WLHIV could inform discussions regarding optimal timing of IPT in women. Our data demonstrates many WLHIV become pregnant during programmatic IPT or initiated IPT during early pregnancy, without standardized surveillance or tracking between routine HIV and pregnancy care. Although uncertainty remains regarding impact of recent trial data and pregnancy recommendations, as new data emerges, approaches to synchronize provision of IPT with regards to routine safe conception and perinatal care will continue to be important [20]. Standardized methods to assess peripartum IPT uptake coupled with surveillance systems could provide further insights on maternal and infant safety outcomes under routine conditions. Availability of shorter course regimens, if found to be safe in pregnancy, may allow continued high initiation and completion during targeted later gestation or early postpartum.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

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FIGURE 1.
Estimated cumulative initiation of isoniazid preventive therapy (IPT) in HIV-infected peripartum women (N = 224).

*For 12 months prior to estimated conception through 6 weeks postpartum 1 tick = 1 week. For >12 months prior to estimated conception 1 tick = approximately 6 months.
Table 1.
Programmatic IPT use and timing of initiation with regards to pregnancy in HIV-infected women

<table>
<thead>
<tr>
<th></th>
<th>n/N (%) or median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any IPT use</td>
<td>224/300 (74.7)</td>
</tr>
<tr>
<td>Current IPT use on enrollment at 6 weeks postpartum</td>
<td>63/224 (28.1)</td>
</tr>
</tbody>
</table>

**IPT use and pregnancy**

<table>
<thead>
<tr>
<th>Use</th>
<th>n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-conception use only†</td>
<td>50/224  (22.3)</td>
</tr>
<tr>
<td>Any pregnancy use</td>
<td>155/224 (69.2)</td>
</tr>
<tr>
<td>Pre-conception extending to pregnancy</td>
<td>45/155  (29.0)</td>
</tr>
<tr>
<td>Pregnancy only</td>
<td>41/155  (26.5)</td>
</tr>
<tr>
<td>Pregnancy extending postpartum</td>
<td>69/155  (44.5)</td>
</tr>
<tr>
<td>Postpartum use only</td>
<td>19/224  (8.5)</td>
</tr>
</tbody>
</table>

**IPT initiation timing and pregnancy**

<table>
<thead>
<tr>
<th>Initiation</th>
<th>n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-conception initiation</td>
<td>95/224  (42.4)</td>
</tr>
<tr>
<td>Median IPT initiation before conception (weeks)</td>
<td>26.6 (11.6–45.3)</td>
</tr>
<tr>
<td>Pregnancy initiation</td>
<td>110/224 (49.1)</td>
</tr>
<tr>
<td>Median gestational age at IPT initiation (weeks)</td>
<td>15.1 (8.3–28.4)</td>
</tr>
<tr>
<td>1st trimester (0 to &lt;14 weeks)</td>
<td>51/110  (46.4)</td>
</tr>
<tr>
<td>2nd trimester (14 to &lt;28 weeks)</td>
<td>30/110  (27.3)</td>
</tr>
<tr>
<td>3rd trimester (≥28 weeks)</td>
<td>29/110  (26.4)</td>
</tr>
<tr>
<td>Postpartum initiation</td>
<td>19/224  (8.5)</td>
</tr>
<tr>
<td>Median IPT initiation after delivery (weeks)</td>
<td>2.5 (1.3–5.9)</td>
</tr>
</tbody>
</table>

* Based on an estimated 38 week (266 day) gestation
† Includes 1 participant who initiated IPT pre-conception, but unknown duration