Commentary: TB Drugs for Pregnant Women with HIV: Challenges, Prospects and Key Research Gaps

Lynne M. Mofenson, M.D.
Senior HIV Technical Advisor
Elizabeth Glaser Pediatric AIDS Foundation
The lack of data on drugs needed to treat important illnesses such as HIV and TB in pregnant and breastfeeding women – and when studied, the long period it takes to obtain such data after a drug is first approved – was and remains unacceptable.
Time from FDA Drug Approval to First Published Pharmacokinetics Data ARVs in Pregnancy


32 approved ARVs in 7 drug classes for adults

Mean knowledge gap 6 years

No published data

- Tenofovir alafenamide
- Doravirine
- Bictegravir
- Ibibalizumab
- Delavirine
- Zalcitabine

Drug approval:
- 0 years: IDV, NVP
- 1 year: AZT, NVP
- 2 years: 3TC, ETV, NFV, TPV
- 3 years: FTC, DTG, RPV, T20
- 4 years: LPV, RTV, EVG, COBI
- 5 years: SQV, RAL
- 6 years: F-APV, EFV
- 7 years: ABC, ddl, d4t, TDF, DRV, MVC, ETV
Data on safety, tolerability, and PK of INH (or other TB drugs) during pregnancy have not been collected or reported systematically, despite TB drugs being available since 1940’s and INH since 1953.

Data are limited, of poor quality, and little comparative data.

Particularly distressing that INH was approved in 1953 but despite extensive search of literature, first data on PK in pregnancy was 2 studies (IMPAACT P1026s, P1078/APPRISE substudy) reported in 2019 (66 year delay!), both suggesting lower levels in pregnancy!
A 2014 systematic review of papers on “tuberculosis and pregnancy” to evaluate studies focusing on TB care for pregnant women up through 2012.

- Only 35 papers identified.

Only 14 studies covered TB treatment in 375 pregnant women, most looking only at treatment outcome.

Only 2 studies were on LBTI prophylaxis (one from 1989).
TB in Pregnancy

- Because data on safety, tolerability, and pharmacokinetics of TB drugs during pregnancy have not been collected or reported systematically, there are inconsistencies in national and international treatment guidelines.

- For example, WHO recommends use of pyrazinamide during pregnancy in 1st line TB therapy but CDC does not, owing to inadequate data on potential adverse fetal effects.

[Table and diagram related to TB treatment in pregnancy]
Because of the lack of studies in pregnancy, first-line tuberculosis drugs were all listed as former US FDA “Pregnancy Category C” (i.e., no adequate well-controlled human studies have been performed, but benefits may be acceptable despite potential risks).

UD= Undetermined (despite many years of use of these drugs)

= teratogenicity in animal repro studies (but no way to systematically collect data on TB drugs in human pregnancy)
WHO consolidated guidelines on drug-resistant tuberculosis treatment

Section 2. The composition of longer MDR-TB regimens

Pregnancy. Amikacin, streptomycin, prothionamide and ethionamide are usually contraindicated during pregnancy. Following the changes made in the 2018 guidelines update, these agents are expected to be used less frequently in future longer regimens. Knowledge about the safety of bedaquiline and delamanid in pregnancy and while breastfeeding is sparse. It is recommended that in such cases, a longer regimen be individualized to include components with a safety profile that is better established. The outcomes of treatment and pregnancy, and postpartum surveillance for congenital anomalies should be documented to help inform future recommendations for MDR-TB treatment during pregnancy.

Section 4. Use of the standardized shorter MDR-TB regimen

Pregnant women. Pregnancy was an exclusion criterion for the STREAM trial. Two of the components of the shorter MDR-TB regimens – the injectable agent and ethionamide (or prothionamide) – are usually contraindicated in pregnancy. Withholding these medicines from the shorter MDR-TB treatment regimen could seriously compromise its effectiveness. In the case of pregnant women, it is therefore recommended that an individualized, longer regimen be used, which can allow the selection of four or more effective medicines with a lower teratogenic risk.

No short regimen permitted in pregnancy (due to NO data)!
MDR TB presents special challenge, because treatment options remain extremely limited as pregnant women are excluded from most new TB drug trials.

### Eight Ongoing or Planned Phase 3 and 4 TB Treatment-Shortening Trials

<table>
<thead>
<tr>
<th>Trial*</th>
<th>TB Type</th>
<th>Drugs in Regimens Under Study</th>
<th>Pregnant Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX-TB (NCT02333799)</td>
<td>XDR</td>
<td>BDQ, LZD, Pa</td>
<td>No</td>
</tr>
<tr>
<td>NEXT (NCT02454206)</td>
<td>MDR</td>
<td>BDQ, LZD, LFX, PYZ, ± HD INH or ETO</td>
<td>No</td>
</tr>
<tr>
<td>TB-PRACTICAL (NCT02589782)</td>
<td>MDR/XDR</td>
<td>BDQ, LZD, Pa, ± MFX or CFZ</td>
<td>No</td>
</tr>
<tr>
<td>STREAM II (NCT02409290)</td>
<td>MDR</td>
<td>CFZ, ETO, MFX, PYZ, INH, KAN, PTO, CFZ, ETO, MFX, PYZ, INH, PTO, BDQ, CFZ, ETO, MFX, PYZ, INH, KAN, PTO, BDQ</td>
<td>No</td>
</tr>
<tr>
<td>STAND (NCT02342886)</td>
<td>DS</td>
<td>Pa, MFX, PYZ</td>
<td>No</td>
</tr>
<tr>
<td>TBTC Study 31 (NCT02410772)</td>
<td>DS</td>
<td>INH, PYZ, HD RPT, ± MFX or ETO</td>
<td>No</td>
</tr>
<tr>
<td>TRUNCATE-TB</td>
<td>DS</td>
<td>INH, PYZ, HD RIF, ± CFZ or LZD, INH, PYZ, RPT, LZD, LFX, INH, PYZ, ETO, LZD, BDQ, INH, PYZ, LZD, LFX, DLM</td>
<td>No</td>
</tr>
<tr>
<td>endTB</td>
<td>MDR</td>
<td>CFZ, DLM, MFX, PYZ, CFZ, BDQ, LFX, LZD, PYZ, CFZ, DLM, LFX, LZD, PYZ, BDQ, LZD, MFX, PYZ, BDQ, DLM, LZD, LFX, PYZ</td>
<td>No</td>
</tr>
</tbody>
</table>

Abbreviations: BDQ, bedaquiline; CFZ, clofazimine; DLM, delamanid; DS-TB, drug-sensitive tuberculosis; E, ethambutol; ETO, ethionamide; HD, high dose; INH, isoniazid; KAN, kanamycin; LFX, levofloxacin; LZD, linezolid; MDR-TB, multidrug-resistant tuberculosis; MFX, moxifloxacin; Pa, protomycin; PTO, prothionamide; PYZ, pyrazinamide; RIF, rifampin; RPT, rifepentine; TBTC, Tuberculosis Trials Consortium; XDR-TB, extensively drug-resistant tuberculosis.

*National Institutes of Health clinical trial identifiers are shown; for more information, go to ClinicalTrials.gov. McKenna L et al. Clin Infect Dis. 2017;65:1383-7
Toward Earlier Inclusion of Pregnant and Postpartum Women in Tuberculosis Drug Trials: Consensus Statements From an International Expert Panel

Table 4. Summary of Consensus Statements

- Pregnant and postpartum women should be eligible for all phase III trials designed for treatment of MDR tuberculosis unless there is a compelling reason for exclusion; aminoglycoside drugs, for example, should be excluded during pregnancy because of their teratogenic potential, but this should not preclude evaluation of other promising new agents.

- Drug companies developing new tuberculosis drugs should be encouraged to complete reproductive toxicity studies early in drug development before beginning phase III trials; these data are needed to adequately inform decisions about the inclusion of pregnant women in subsequent clinical trials.

- Specific trials of shortened treatment regimens for LTBI should be designed for pregnant women to facilitate treatment completion of regimens and reduce the risk of progression to tuberculosis disease during the high-risk pregnancy/postpartum period.

- Targeted PK studies in pregnant and postpartum women should be nested into all trials to provide data on appropriate dosing of drugs during pregnancy and postpartum, when evidence-based dosing guidelines are not already available and particularly when pregnancy is likely to have a significant impact on drug disposition.

- A registry should be established to accumulate data on the outcomes of pregnancies exposed to any tuberculosis drugs to allow monitoring of adverse events and to provide data to inform inclusion of pregnant women in clinical trials.

Abbreviations: LTBI, latent tuberculosis infection; MDR, multi-drug resistant; PK, pharmacokinetic.
Clinical Trial Drug Development Phases, with Focus on Drugs That Will Be Used in Pregnancy

Non-Pregnant

- Pharmacokinetics, safety, tolerability
- Pharmacodynamics, dose range
- Definitive dose, efficacy
- Efficacy, comparison to standard of care

Pregnant, Current Status of Studies

- Not included
- Not included
- Not included
- Generally not included; if woman becomes pregnant, stops drug, often comes off study

Pregnant, Proposed Status of Studies

- Not included → exception: life-threatening conditions with no treatment available (e.g., Ebola)
- Not included → exception: life-threatening conditions with no treatment available (e.g., Ebola)
- Pharmacokinetic studies in parallel to phase IIb in pregnant women with limited options and hence favorable benefit/risk
- If pharmacokinetic study not done, conduct in parallel to or as substudy of phase III

PHASE I

Animal repro-tox usually completed

PHASE IIa

Animal repro-tox studies done

PHASE IIb

PHASE III

Animal repro-tox usually completed

PHASE IV

Post-market approval surveillance, safety, rare events

Pharmacokinetic pregnancy study may or may not be done; post-market safety surveillance may or may not be done

If pharmacokinetic study during phase IIb, enroll directly into phase III trials

If pharmacokinetic study not done, conduct in parallel to or as substudy of phase III

Once safe dose, enroll in phase III trials

If have pharmacokinetic data, potential comparison to standard regimen used in pregnancy (safety)
Importance of Pharmacovigilance: Preconception Dolutegravir (DTG) and Neural Tube Defects (NTD)

- Birth surveillance for major surface birth defects at 15 maternity wards in Botswana in HIV-positive and HIV-uninfected women.
- Initially designed to evaluate the risk of NTD with preconception efavirenz exposure; Botswana moved to first-line DTG, so program able to assess preconception DTG exposure as well.
- Statistically significant prevalence difference for NTD between preconception DTG and other comparison groups.

<table>
<thead>
<tr>
<th></th>
<th>March 2019 #NTD/#exposures</th>
<th>NTD Prevalence</th>
<th>Prevalence Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preconception DTG</td>
<td>5/1,683</td>
<td>0.3%</td>
<td>-</td>
</tr>
<tr>
<td>Preconception Non-DTG</td>
<td>15/14,729</td>
<td>0.11%</td>
<td>0.20 (0.01-0.59)</td>
</tr>
<tr>
<td>Preconception EFV</td>
<td>3/7,959</td>
<td>0.04%</td>
<td>0.26 (0.07-0.66)</td>
</tr>
<tr>
<td>HIV-uninfected</td>
<td>70/89,372</td>
<td>0.08%</td>
<td>0.22 (0.05-0.61)</td>
</tr>
</tbody>
</table>
What is In Place for Pharmacovigilance for Drugs in Pregnancy?

### HIV Drugs

- Data on 57 brand ARV drugs and 93 generic formulations of the brand drugs.
- Enrolls ~1,300 women a year into prospective global registry.

### TB Drugs

![Summary of Birth Defects among First Trimester Exposures, Prospective Registry Cases Closed with Outcome through 31 July 2019](image)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Number of Births</th>
<th>Prevalence (%)</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamivudine</td>
<td>1847</td>
<td>2.56</td>
<td>2.00</td>
<td>3.20</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>1346</td>
<td>2.45</td>
<td>1.89</td>
<td>3.23</td>
</tr>
<tr>
<td>NVP</td>
<td>2840</td>
<td>1.97</td>
<td>1.61</td>
<td>2.40</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>1492</td>
<td>2.25</td>
<td>1.81</td>
<td>2.75</td>
</tr>
<tr>
<td>Abacavir</td>
<td>972</td>
<td>2.34</td>
<td>1.95</td>
<td>2.74</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>1042</td>
<td>2.37</td>
<td>1.89</td>
<td>2.90</td>
</tr>
<tr>
<td>Stavudine</td>
<td>1324</td>
<td>2.80</td>
<td>2.34</td>
<td>3.29</td>
</tr>
<tr>
<td>Zalcitabine</td>
<td>1346</td>
<td>2.82</td>
<td>2.22</td>
<td>3.50</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>523</td>
<td>3.13</td>
<td>2.55</td>
<td>3.73</td>
</tr>
</tbody>
</table>

Figure 1: Summary of Birth Defects among First Trimester Exposures, Prospective Registry Cases Closed with Outcome through 31 July 2019
Historic Perspective on Drug Use in Pregnancy

- One picture to sum it up:

- Update:

  → Lessons learned: As new drugs are developed for treatment & prevention of HIV/TB (and other significant diseases occurring in pregnancy), studies in pregnant & breastfeeding women are critical and need to be conducted early for promising drugs.