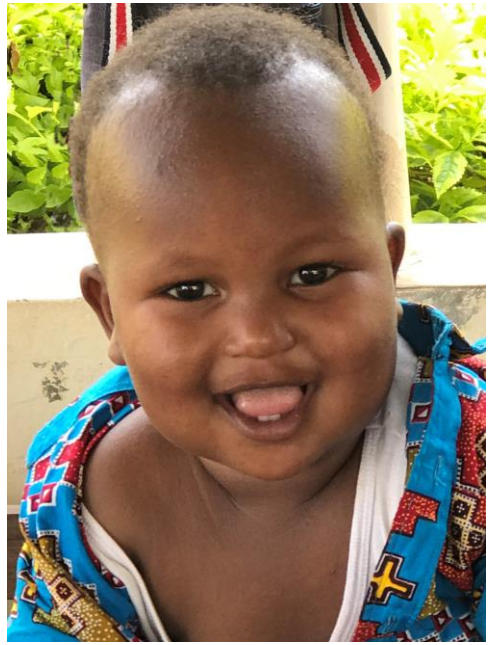


SETTING THE SCENE ON RESEARCH AND DEVELOPMENT RELATED TO TUBERCULOSIS FOR PREGNANT AND POSTPARTUM WOMEN

Stellenbosch UNIVERSITY IYUNIVESITHI UNIVERSITEIT
forward together
sonke siya phambili
saam vorentoe

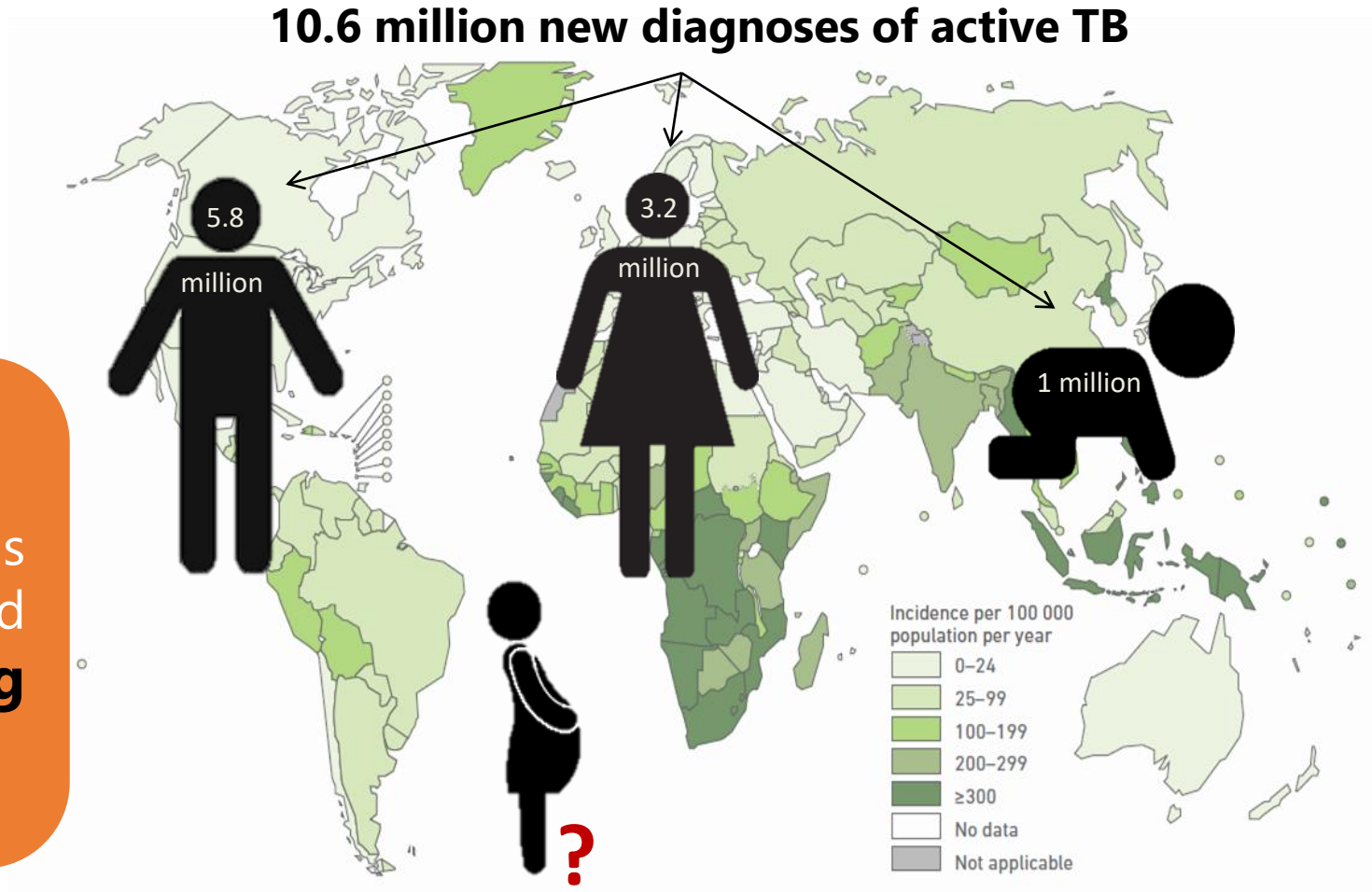
Anneke C. Hesseling, Desmond Tutu TB Centre, Stellenbosch University, South Africa

DESMOND TUTU TB CENTRE · SENTRUM · IZIKO
UNIVERSITY STELLENBOSCH UNIVERSITEIT
Every breath counts

5-7 December 2022, Vatican City

BURDEN OF TB DURING PREGNANCY ?

TB burden during pregnancy is likely high but not well-quantifed
Urgent need for reporting



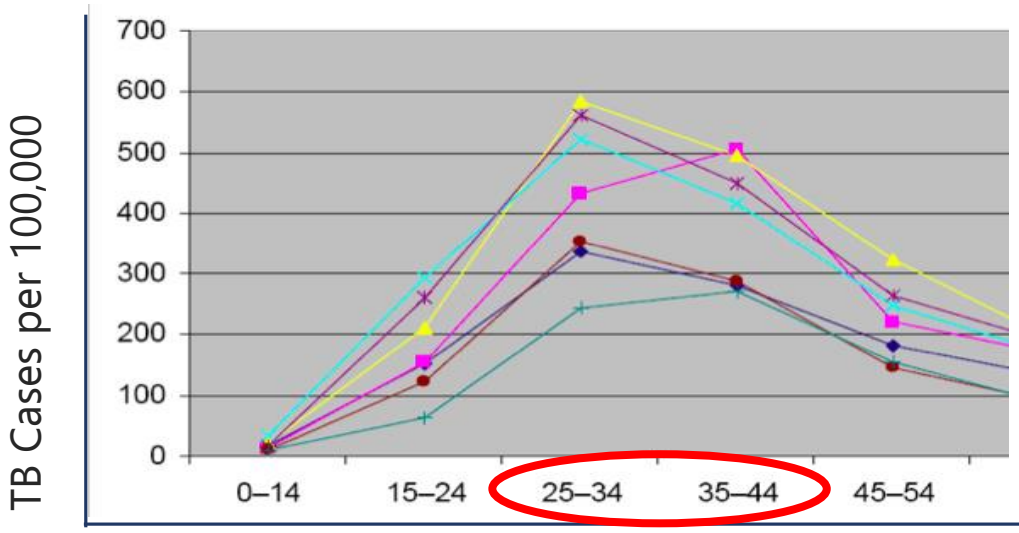
Sugarman Lancet Global Health 2014

WHO 2022

TB INCIDENCE PEAKS DURING THE REPRODUCTIVE AGE, IRRESPECTIVE OF HIV STATUS

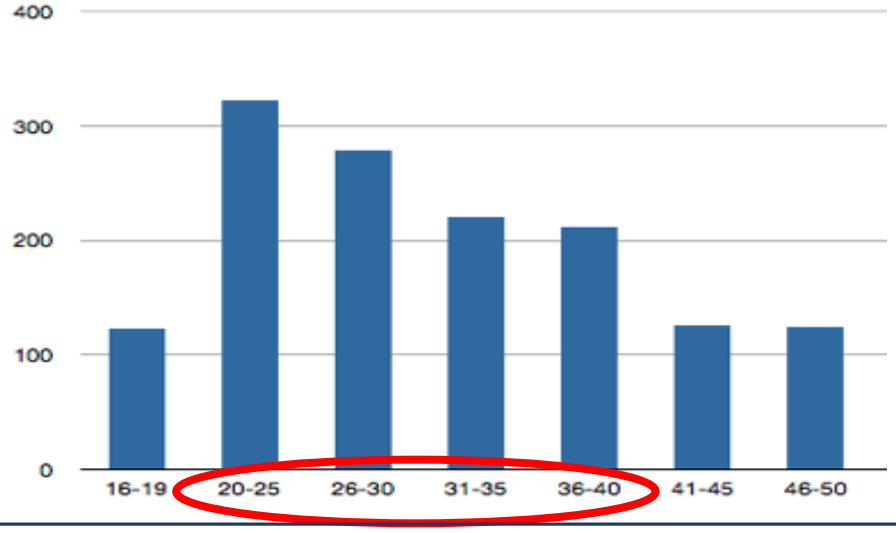
Women in sub-Saharan Africa

Deluca JAIDS 2009



Women in India

RNTCP Gender differentials in TB control 2004



Age Group

INCREASED ADVERSE OUTCOMES WITH TB DURING PREGNANCY

3384 pregnancies with active TB and 119 448 without TB included

Mortality* **4-fold**

Morbidity **3-fold**

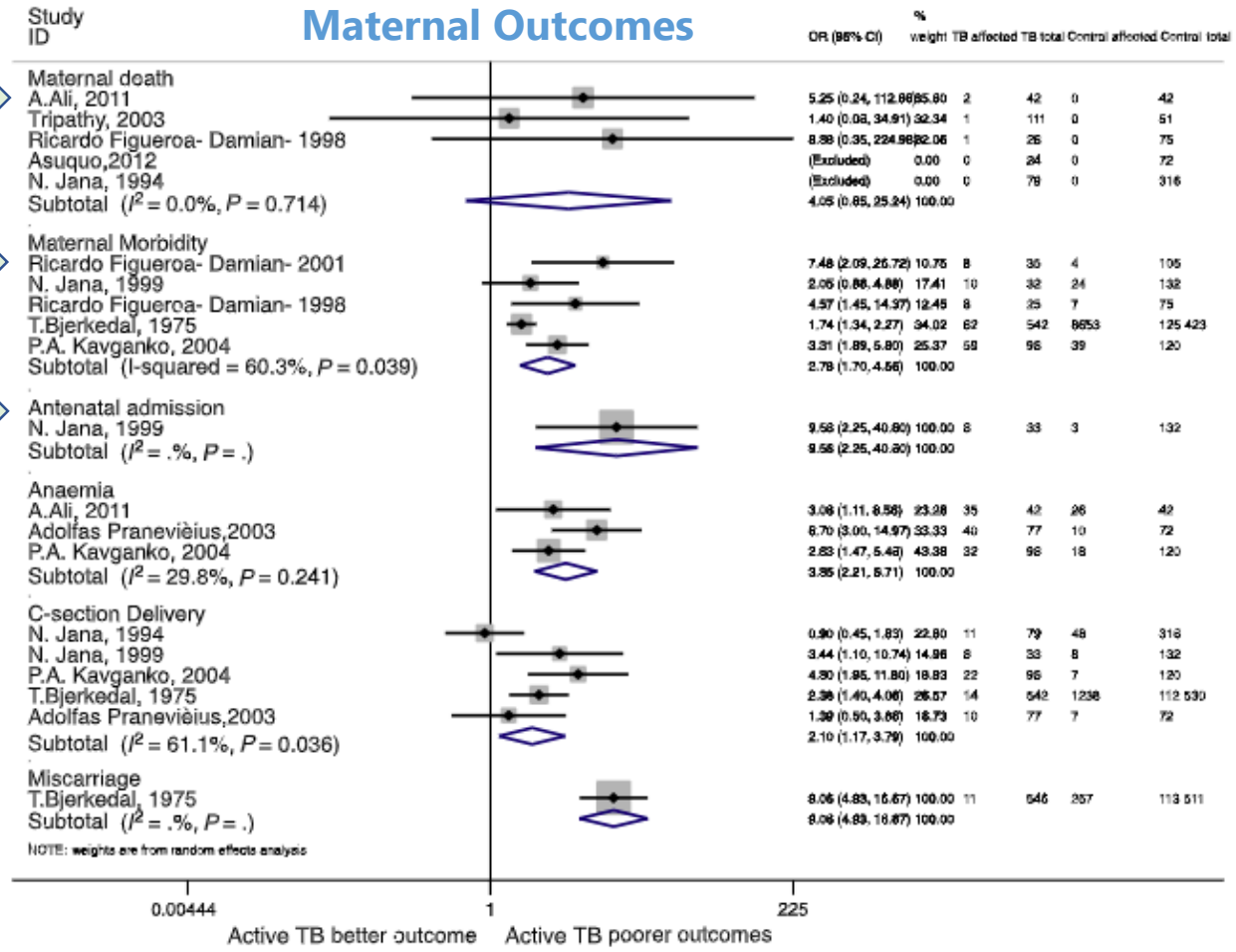
Hospitalization **10-fold**

Anemia **4-fold**

C-section **2-fold**

Miscarriage **9-fold**

*not significant



Sobhy BJOG 2017

HISTORICAL PARADIGM

1. Historically, **pregnant and postpartum** women have been **systematically excluded** from trials on prevention and treatment of TB because of the potential teratogenic risks of new medications and the perceived complexity of studying pregnant women in trials.
2. This approach has resulted **in a lack of access** to much-needed TB treatment and prevention regimens and agents, resulting in potential harm for women and their infants.
3. Most newer TB medications and regimens for prevention and treatment are **used off-label** in pregnant women, without any appropriate dosing or safety data in pregnancy, putting mothers and infants at risk.
4. Routine **national TB surveillance systems currently do not capture data** or report to WHO on pregnancy status for TB preventive therapy or for TB treatment, resulting in limited data on TB treatment outcomes in women and their infants.

FIRSTLINE DRUGS FOR TB IN PREGNANCY

Drug	FDA	Crosses placenta	Breast-feeding	Issues in pregnant women
INH	C	Yes	Yes	Hepatotoxicity
Rifampicin	C	Yes	Yes	Drug interactions with NVP, PIs, OCPs; may require Vit K
Rifabutin	B	Unknown	Unknown	Drug interactions with PIs, limited experience
EMB	B	Yes	Yes	
PZA	C	Unknown	Unknown	Different guidance

Brost Obstet Gyn Clin 1997;Bothamley Drug Safety 2001;Shin CID 2003; Micromedex; Mathad & Gupta CID 2012; Gupta PloSMed 2019

Management of Drug-Resistant Tuberculosis in Pregnant and Peripartum People:

A FIELD GUIDE

First Edition, September 2022

Photo courtesy of Chris Tabu at @TabuCapital

But: WHO evidence-based guidelines needed for NTPs to implement

PARADIGM SHIFT NEEDED: OVERARCHING PRINCIPLES

I. Therapeutics

1. **For all priority existing licensed or routinely used TB drugs**, the PK and safety of should be studied in pregnant women across therapeutic indications (TB prevention, disease, DS- and DR-TB)

2. **For new drugs/regimens:** non-clinical developmental and reproductive toxicology studies should be conducted earlier during drug development for all new TB drugs/regimens.

   Fertility and early embryonic development and embryo-fetal development studies should be completed during or no later than the end of Phase 2 registrational trials.

3. **Prenatal and postnatal development** studies should be completed during early Phase 3 or no later than the end of Phase 3 registrational trials

The research community, funders, industry and regulators should urgently address these research gaps in ongoing and future work for all priority first-line and licensed 2nd line drugs.

4. **Consultation needed with TB trial research groups, community stakeholders and regulatory authorities to inform research priorities and better understand pregnant women's preferences for TB prevention and treatment (and infants).**

   Women of childbearing potential affected by TB should, themselves, be involved in the identification of priority research questions, study design, recruitment, conduct and dissemination of results. Targeted qualitive research amongst pregnant women affected by TB should be undertaken by research groups in close collaboration with civil society.

Researchers, civil society, funders should collaborate on designing key data elements and ensure that such data is collected in consultation with pregnant women

5. **New TB regimens for prevention and treatment: pregnant women should be included earlier in therapeutic trials.** The inclusion of pregnant women should be considered early in the design and implementation of TB trials, with a careful risk-benefit assessment for the timely inclusion and methods to do so. Pregnant women should be enrolled in specific studies to determine pregnancy PK and preliminary safety for high-priority TB drugs and regimens as soon as non-clinical prenatal and postnatal development (PPND) studies are completed with no negative signals.

Researchers, funders and regulators should collaborate to make the timely inclusion pf pregnant women in TB trials a minimum requirement.

6. **A pregnancy implementation plan should be developed early on, as for children**

Regulators should request such a plan early on from industry, while adult phase 2 trials are being planned and implemented

7. **Women who become pregnant in pre-licensure trials should be given the option to make an informed choice to stay on study drug(s) (with reconsent) and** contribute pregnancy PK and safety data if the two following conditions are met: (1) non-clinical fertility and early embryonic development (FEED) and embryo-fetal development EFD studies are completed, with no negative signals; and (2) dosing is established in non-pregnant adults.

Research groups, funders, regulators and civil society should ensure that this option is included in any therapeutic trial

8. **Experts on TB in pregnancy should be included in expert groups** (e.g WHO Target Regimen Profiles for Tuberculosis Treatment, similar to the Conferences on Antiretroviral Drug Optimization (CADO) and the Pediatric Antiretroviral Drug Optimization (PADO) groups) to identify "high-priority" TB drug regimens for pregnant people, as for non-pregnant people, as is the case for children and adolescents. Experts should also be included in panels deliberating UNHLM requests to ensure that governments undertake commitments relevant to pregnant women affected by TB.

Policy makers including WHO and others should include experts and researchers in maternal TB, in addition to paediatric TB, in such panels. . NTPs should report on progress made on TB indicators for pregnant and postpartum women

SPECIFIC PRIORITY TB TREATMENT RESEARCH GAPS

1. **PK and safety data on all priority first line and all licensed 2nd line TB drugs** used as standard of care should be urgently determined and shared, where lacking. Researchers and funders should undertake PK and safety studies which include pregnant and postpartum women receiving bedaquiline, delamanid, levofloxacin, moxifloxacin, linezolid, clofazimine, terizidone and rifapentine
2. **Drug-resistant TB: BPAL and BPAL-M**: 6 -month all oral treatment of MDR and XDR-TB in adults: there is an urgent need for PK and safety data and pregnancy outcomes
3. **Drug-susceptible: TB (4-month TBTC Study 31 short regimen regimen):** Rifapentine + HZE/ RPT+Moxi +HZ Researchers, regulators and funders should have a consultation which incudes pregnant women, on the risk/benefit studying pregnant women on this regimen
4. **Drug-susceptible TB infection**: The PK and safety of 1HP and 3HP should be studied as a priority Researchers and funders should undertake trials on the safety, PK and effectiveness of 1 HP and 3 HP during pregnancy
5. **Drug-resistant TB infection**: The PK and safety data on delamanid and levofloxacin should be studied in pregnant and postpartum women as a priority

WHO, regulators, funders, civil society and industry should work with researchers to generate this data as a priority

II. TB VACCINE RESEARCH

An unprecedented number of TB vaccine candidates already in or soon to enter phase III trials, the following are key priorities:

1. **TB vaccine developers should commit a combined cross-study effort to collect standardized information on maternal, infant, and pregnancy outcomes** among women who become pregnant after enrolling in vaccine studies.
2. **TB vaccine developers should design for inclusion by committing to generate supporting evidence,** early enough to enable the inclusion of pregnant women in efficacy trials.
3. **TB vaccine developers should commit to collecting improved data on TB incidence and IGRA status during pregnancy**, by incorporating pregnancy into the preparatory epidemiological studies that will precede phase III trials.

TB vaccine developers, researchers and regulators should prioritize the earlier inclusion of pregnant women in TB vaccine trials and jointly develop a standard approach (master protocol) for inclusion and data collection

III. PROGRAMME IMPLEMENTATION & SURVEILLANCE: BETTER DATA ON BURDEN OF DISEASE AND TPT

1. Surveillance data on TB and pregnancy and the postpartum period, including treatment outcomes. should urgently be included in NTPs and in clinical research, where more detailed data can be collected. NTPs should consider including pregnancy status and trimester as an indicator in TB treatment and TPT registers. Where feasible, pilot or demonstration projects should be implemented to assess the feasibility and utility of such data.

- WHO and NTPs should work towards inclusion of pregnancy indicators for TPT and TB treatment . This will improve estimated of burden of disease. TPT numbers and market is 20-fold vs. TB treatment market

- WHO and researchers should ensure that planned WHO-commissioned global data curation on TB and MDR-TB IPD and meta-analysis in adults, adolescents and children should also include pregnant women

2. WHO and NTPs should ensure that current TB screening recommendation relevant to pregnant women in current WHO TB screening guidelines:
https://www.who.int/publications/i/item/9789240022676) are better implemented and tracked

WHO and NTPs should improve screening for TB in pregnant and postpartum women as per current recommended WHO screening guidelines

3. Researchers and industry should be encouraged to more systematically report on pregnancy safety data and contribute data through the development of a <u>centrally coordinated global TB pregnancy registry.</u>

This should include pregnant women included in trials and women who become pregnant on studies. Data should include TB treatment outcomes, maternal and infant outcomes (clinical trials and observational studies). Active surveillance should be expanded to collect better quality drug safety in pregnancy to enable systematic and rapid detection of adverse maternal, pregnancy and birth outcomes, especially rare events, such as birth defects.

Regulators, industry and researchers should urgently collaborate and share data to support the implementation of a centrally coordinated global trial registry for TB during pregnancy and the postpartum period

The "Wish List"

Pregnancy

Gestational age

Postpartum

Infant outcome

PARADIGM SHIFT UNDERWAY? CALL TO ACTION

- Multiple stakeholders are now expressing concerns around the exclusion of pregnant and postpartum women from pre- and post-licensure TB drug and vaccine trials and the negative consequences to mothers and infants

This requires cross-sector stakeholder approach

Clinical Infectious Diseases

VIEWPOINTS

IDSA Infectious Diseases Society of America

hivma hiv medicine association

OXFORD

Toward Earlier Inclusion of Pregnant and Postpartum Women in Tuberculosis Drug Trials: Consensus Statements From an International Expert Panel

Amita Gupta,[1,a] Jyoti S. Mathad,[8,a] Susan M. Abdel-Rahman,[9] Jessica D. Albano,[10] Radu Botgros,[18] Vikki Brown,[11] Renee S. Browning,[3] Liza Dawson,[3] Kelly E. Dooley,[2] Devasena Gnanashanmugam,[3] Beatriz Grinsztejn,[19] Sonia Hernandez-Diaz,[13] Patrick Jean-Philippe,[4] Peter Kim,[3] Anne D. Lyerly,[12] Mark Mirochnick,[15] Lynne M. Mofenson,[5] Grace Montepiedra,[14] Jeanna Piper,[3] Leyla Sahin,[7] Radojka Savic,[16] Betsy Smith,[3] Hans Spiegel,[4] Soumya Swaminathan,[20] D. Heather Watts,[17] and Amina White[6]

NIH sponsored workshop

Gupta, CID 2016

END TB MDR TB TRIAL EXAMPLE

endTB Clinical Trial Participant Information Leaflet: Pregnant Participants
v3.4 – 31 July 2020

Bedaquiline

Bedaquiline is generally well tolerated with few side effects. Its use is associated with changes in heart electricity described above (called 'QT prolongation'), but this almost never has symptoms, and only very rarely requires a change in treatment. Bedaquiline interacts with a number of other drugs, including antiretrovirals, and your doctor will discuss which drugs are not allowed to be taken with bedaquiline. You should take bedaquiline with food.

The drug packaging reports no studies of bedaquiline in pregnant women. Animal studies of bedaquiline did not find harm caused to babies or reproduction. Bedaquiline is a new drug and the experience with its use in pregnant women is limited. Howe advised in pregnant women with tuberculosis as benefits frequer

endTB Clinical Trial Information Leaflet

for participants who are considering continued trial participation after becoming pregnant

Delamanid

Delamanid is usually well-tolerated. The most common side effects are gastrointestinal problems, but some people also report anxiety and tremor. Delamanid should be taken with food.

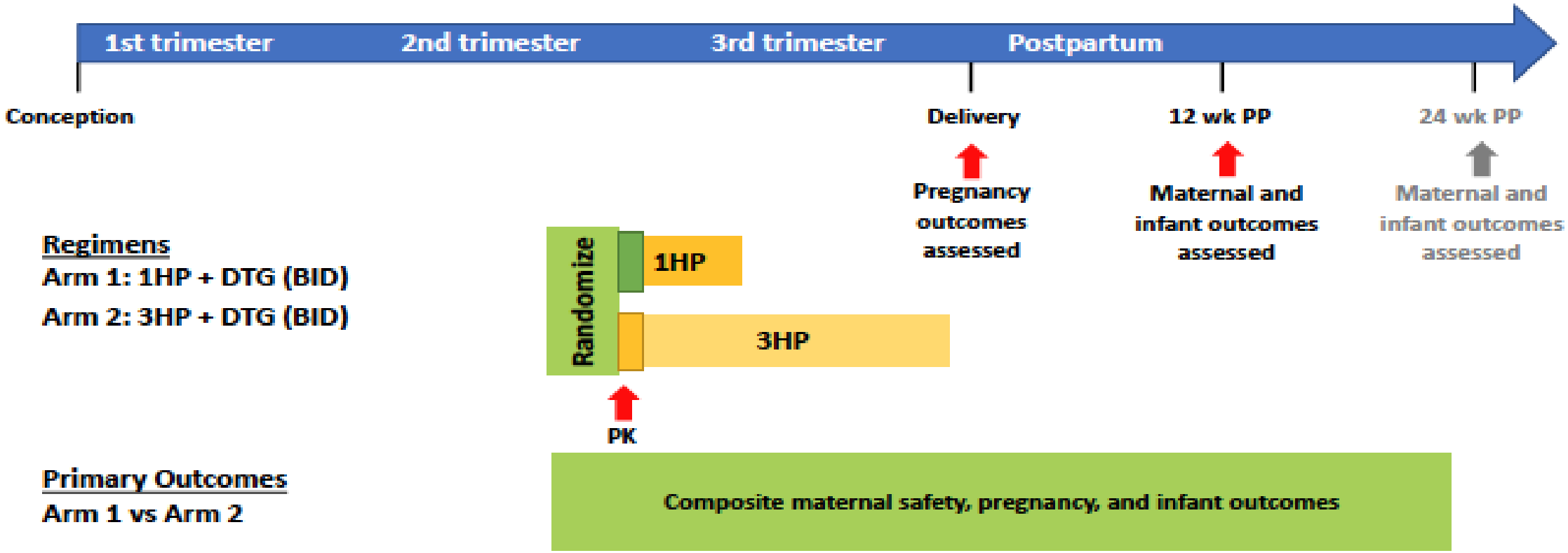
The drug packaging reports no studies of delamanid in pregnant women. Animal studies of delamanid have shown an increased risk of malformations in developing rabbits. Delamanid is a new drug and the experience with its use in pregnant women is limited. However, because safer treatment alternatives are very limited in pregnant women with fluoroquinolone-resistant tuberculosis, benefits may warrant use of the drug, despite potential risks.

Pyrazinamide

Pyrazinamide can cause joint pain and/or swelling, which with symptomatic treatment.

The drug packaging reports no studies of pyrazinamide in pregnant women. Animal reproduction studies have not been conducted with pyrazinamide. However, there is a lot of experience with the use of this drug as part of first-line tuberculosis treatment, including in pregnant women. Therefore, the use of this drug is often advised in pregnant women with tuberculosis as benefits frequently outweigh potential risks.

DOLPHIN MOMS



Interim PK analysis after 1st 25 participants enrolled in each Arm have completed Day 17 sparse PK visit and data reviewed

PK measures/timing: Sparse PK sampling for DTG: ka, VD, Cl/F, inter-subject variability; post-hoc Bayesian predictions of PK parameters of DTG including AUC24 and Ct, following HP dosing.

Arm 1: Day 1 in AM prior to 1HP and DTG AM dose, Day 17 prior to DTG dose (track with 72 hours after 3rd dose of HP in Arm 2), plasma for RPT PK Day 17

Arm 2: Day 1 in AM prior to 1HP and DTG AM dose, Day 17 prior to DTG dose (72 hours after 3rd dose of HP), Day 52 prior to DTG dosing (72 hours after 8th dose of HP)

PP, postpartum; HP, Isoniazid and rifapentine

ACKNOWLEDGEMENTS

Jyoti Mathad, Amita Gupta, Elaine Abrams, Marianne Loveday, Lindsay McKenna, Marije van Schalkwyk, Kerri Viney, Sabine Verkuijl, Annemieke Brands, Sizulu Moyo

In memoriam
Desmond Tutu
Archbishop Emeritus