Better, earlier pregnancy and lactation data for new HIV drugs: how do we get there?

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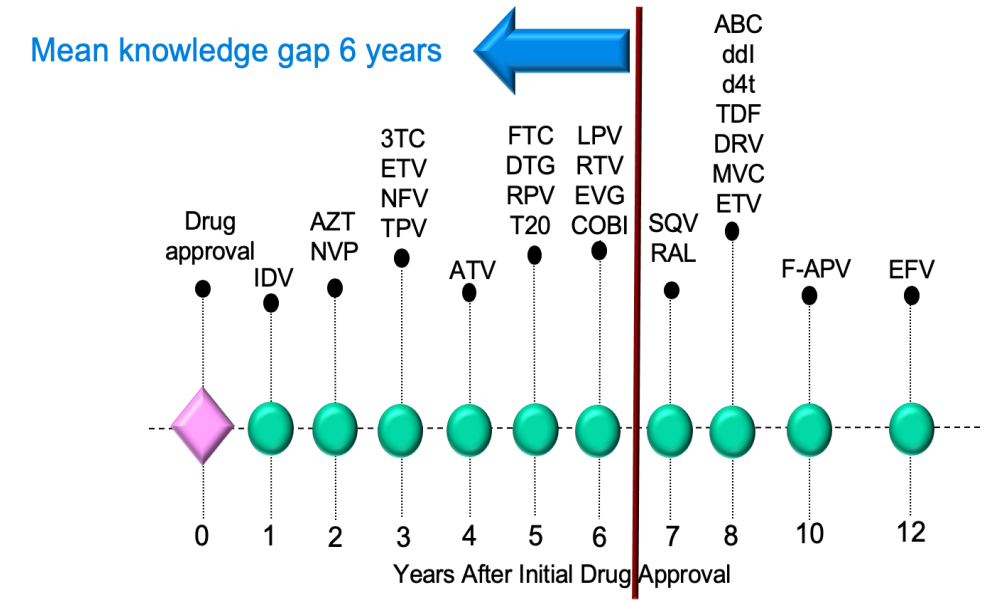
What is the problem?

- 1920-2010: **>90%** of FDA-approved drugs had **no data** on safety/efficacy in pregnancy
- **>80%** of women take a drug in pregnancy with **minimal safety/efficacy data**
- Even when pregnancy PK data exist for ARVs, median **6 years** from licensure to published data, which often are minimal
- **Absence of (or inadequate) data** exposes women / fetuses to **potential harms: toxicities, inferior treatment**
- **Exclusion** of pregnant women from research **does NOT remove risk,** but simply **shifts risk** from a setting with informed consent and intensive monitoring **to routine clinical setting**

Time from FDA Drug Approval to First Published Pharmacokinetics Data in Pregnancy

modified from: Colbers A et al. Clin Infect Dis 2019 (epub ahead of print)

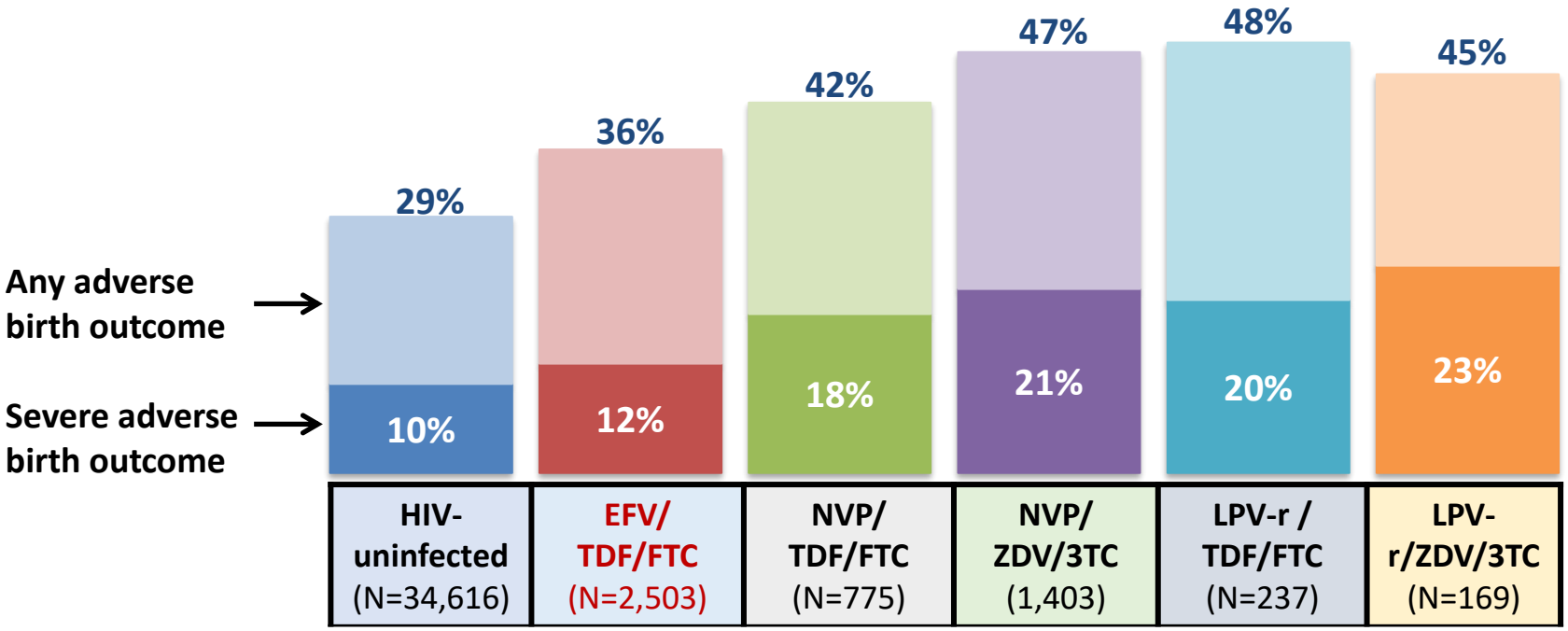


Real-world examples of harm due to absence of high-quality pregnancy data

- **Focus** is often on the **potential harm of taking drugs, but NOT taking** optimal drugs during pregnancy due to lack of data **can cause harm** to mother and fetus
- **Non-HIV example** of harm: depression
- **HIV example:** ~3-year delay (~2010 to 2013) in moving from nevirapine- to efavirenz (EFV)-based ART for women living with HIV (WLHIV) due to concern for neural tube defects (NTDs), based primarily on non-human primate data
    - No evidence of elevated risk of NTDs with EFV, in subsequent human data

Older ARV regimens associated with substantially higher rates of adverse birth outcomes than EFV-based ART

Botswana Tsepamo surveillance study 2014-2016 *(Zash et al)*



Slide adapted from Rebecca Zash

What is the status quo for collecting data on new drugs in pregnancy?

Current approach aims primarily to **protect the fetus/infant** from harm

Minimal incentives (but **many dis-incentives**) for industry and researchers to include pregnant/lactating women (PLW) in trials, including liability concerns

Pre-clinical reproductive toxicity data often not available until **late** in drug development

Most current pregnancy/lactation data arise from **postmarketing opportunistic studies** of women receiving antiretroviral (ARV) for clinical care

Some (minimal) systematic **post-marketing surveillance** or observational studies evaluate pregnancy and other outcomes following drug licensure

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Most current pregnancy/lactation data arise from **postmarketing opportunistic studies** of women receiving the ARV of interest for clinical care

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It is time to improve on the status quo, and work toward collecting high-quality timely pregnancy data for new ARVs

CATCH-22: CLINICAL TRIAL EDITION

What is happening to address lack of pregnancy data for medications in the US, in general?

PRGLAC*: Task Force on Research Specific to Pregnant and Lactating Women

NIH/NICHD, CDC, HHS, FDA, medical societies, non-profits, industry.
"Federal policy should be revised to require inclusion or a scientific justification for exclusion of pregnant women and lactating women in clinical research, absent compelling reasons for their exclusion"

CDC Treating for Two: Safer Medication Use in Pregnancy

Initiative to expand/accelerate research on medication use/safety in pregnancy; provide guidance and data to patients and providers

OHRP 2018

Common Rule no longer includes pregnant women as a vulnerable research population

PRGLAC: 1) Include and integrate pregnant women and lactating women in the clinical research agenda, 2) Increase the quantity, quality, and timeliness of research on safety/efficacy of drugs used by pregnant /lactating women, 3) Increase the quantity, quality, and timeliness of research on safety and efficacy of therapeutic products used by pregnant women and lactating women, 4) Expand the workforce of clinicians and research investigators with expertise

What is happening to address lack of pregnancy data for ARVs?

WHO
PADO4 meeting to review gaps, identify priorities for enabling drug optimization for PLW (Dec 2018)

WHO/IMPAACT
Workshop on approaches to studying ARV pharmacokinetics in PLW (June 2019)

IAS/CIPHER
Meeting with industry to understand barriers to / facilitators of including PLW in research (July 2019)

UP NEXT: WHO/IMPAACT
Work toward consensus on approaches to studying new ARVs in PLW (June 2020)

Stakeholders involved thus far:

- WHO
- IAS
- NIH
- Community
- IMPAACT
- PANNA
- Researchers
- FDA, EMA
- Industry
- PHASES/ ethicists
- CIPHER
- NGOs, clinicians

Potential framework for studying new ARVs in pregnancy

Note: Much of the proposed framework has been articulated by others, e.g. Roes (Netherlands), and further discussed at WHO/IMPAACT workshop July 2019; some represents my own views, and all of it is in evolution

Outline of typical clinical trial drug development phases

Non-Pregnant	**Pharmacokinetics, safety, tolerability**	**Pharmaco-dynamics, dose range**	**Definitive dose, efficacy**	**Efficacy, comparison to standard of care**	**Post-market approval surveillance, safety, rare events**

Adapted from figure prepared by Lynne Mofenson

Drug development phases: current timing of pregnancy studies

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Pregnant, Current Status of Studies	**Not included**	**Not included**	**Not included**	**Rarely included**	**Post-licensure: Phase I pregnancy study may or may not be done; safety surveillance may or may not be done**

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Pregnant, proposed approach to studies	**Only if life-threatening condition with no treatment available (e.g., Ebola)**	**Only if life-threatening condition with no treatment available (e.g., Ebola)**	**Only if limited options in pregnancy and hence favorable benefit/risk**	**→ Phase I in pregnant women living with HIV →Once have dose, phase II/III trials in pregnant women**	**Pregnancy trials, if not done earlier; pharmacovigilance**

Adapted from figure prepared by Lynne Mofenson

How might such acceleration of pregnancy data for new ARVs be implemented?

Suggested approaches to implementation

Facilitate acceleration:

- Reproductive toxicity studies early in drug dev’t
- Work with IRBs, researchers, to update norms
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Conduct earlier pregnancy PK study (prior to drug licensure)

- **Women who become pregnant in Phase II/III trials: if give informed consent, stay on study drug (unless concern raised by pre-clinical or early clinical data) to contribute pregnancy PK and safety data via standardized protocol, *and/or***
- **Conduct small separate pregnancy PK/safety study during Phase III in non-pregnant**

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Conduct earlier pregnancy PK study (prior to drug licensure)

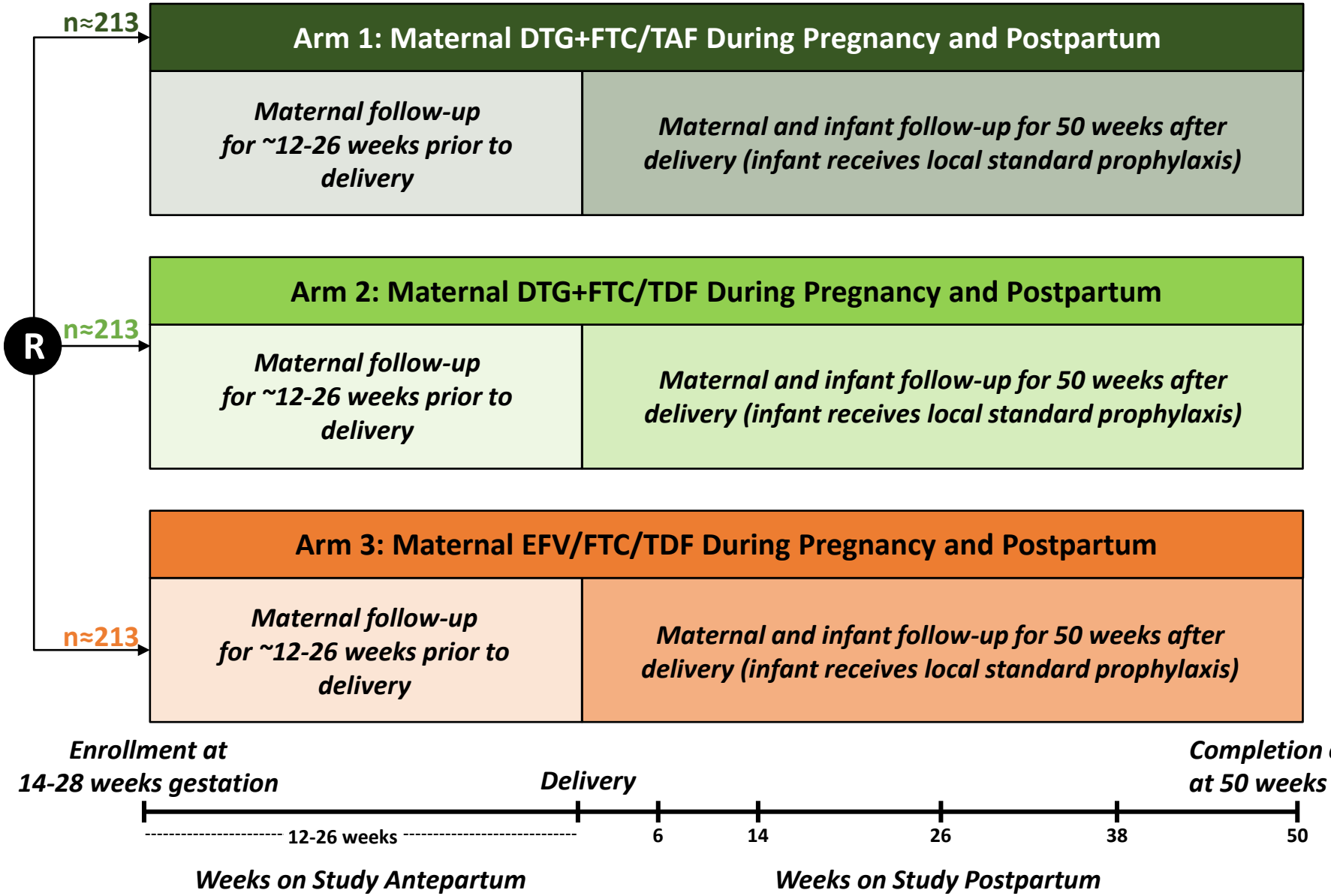
- Women who become pregnant in Phase II/III trials: if give informed consent, stay on study drug (unless concern raised by pre-clinical or other data) and contribute pregnancy PK and safety data
- Conduct small separate pregnancy PK/safety study during Phase III in non-pregnant

Clinical trial in pregnant women while Phase III trial ongoing in non-pregnant

- **Once have sufficient PK/safety data from small number of pregnant women**
- **Conduct separate larger parallel trial in pregnant women or enroll pregnant women directly into Phase III trial, alongside non-pregnant participants**
- **Consider adaptive and novel designs**

Note: primary outcomes of interest from clinical HIV treatment trials in pregnancy are **safety, not efficacy** (in most cases)

IMPAACT 2010 (VESTED) Study Design



Oral presentation
Dr. Lameck Chinula,

This and other trials have demonstrated that large numbers of pregnant WLHIV choose to take part in clinical trials

Relevant toxicity outcomes in women in pregnancy

ARV toxicities of more concern in women during pregnancy/postpartum, from prior data	Outcome measures
• Nausea/vomiting/diarrhea: LPV/r (PROMOTE, Cohan 2015)	• Weight gain, GI symptoms
• Hypertension: NVP (Tsepamo, Zash 2018) • pre-eclampsia with any ART (compared with no ART)	• Pre-eclampsia/eclampsia • Gestational hypertension
• Postpartum depression: EFV (Jones AIDS Behavior 2018)	• Psychiatric events
• Hepatotoxicity: ? nevirapine; raltegravir (case report) (Renet J Ob/Gyn Canada 2013)	• Liver disease/injury
• Neutropenia: ZDV (Chasela NEJM 2010)	• Hematologic toxicities
• Hypothetically: gestational diabetes (e.g. with DTG)	• Gestational diabetes

ARV efficacy in pregnancy

Virologic efficacy of ARVs in pregnancy	Outcome measures
• Most ARVs maintain similar virologic efficacy (exceed target exposure) in pregnancy, even if AUC reduced in 2nd/3rd trimesters vs. postpartum (e.g. EFV, TDF, FTC, LPV/r, nelfinavir, darunavir, RAL, DTG) • Rare exceptions: cobi-boosted ATV, DRV, ELV; RIL (AUC 20%-50% lower, trough a/w detectable VL) • MTCT prevention: very low MTCT with suppressed VL on ART; minimal differences between ART regimens thus far	**General recommendation: unless pregnancy PK data raise concern, probably do not need extensive efficacy data for ARVs used in treatment**
• **ARVs used for HIV prevention, or entirely new drug classes**	***May* need to study efficacy**

Adverse pregnancy outcomes

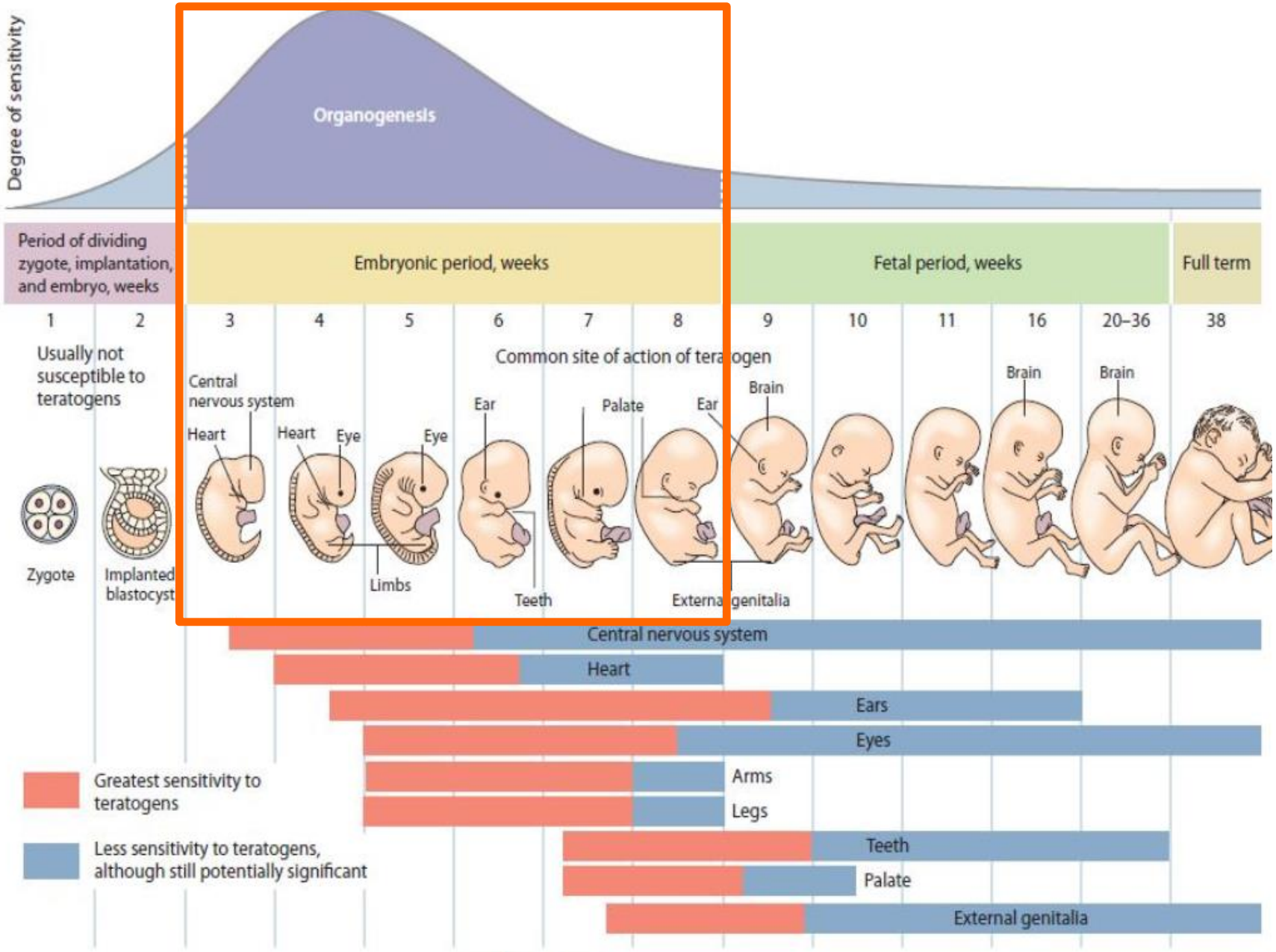
Adverse pregnancy outcomes previously found to vary by ARV	Outcome measures
• Preterm or very preterm delivery: protease inhibitors (Mma Bana, PHACS/SMARTT, PROMISE, others)	• EGA at delivery
• Stillbirth: NVP/ZDV/3TC (Tsepamo, associated with htn)	• Birth outcome
• Low birth wt/small for gestational age (SGA): NVP & LPV/r)	• Birthweight, EGA
• Neonatal death: LPV/r/TDF/FTC, a/w very preterm (PROMISE)	• Mortality by 28 days
With from-conception /1st trimester exposure	
• Congenital anomaly: 1st trimester nelfinavir, ddI (APR), atazanavir, ddI/d4T (PHACS/SMARTT); NTD with DTG (Tsepamo)	• Systematic exam for anomaly
• Spontaneous abortion: particularly challenging to measure	• SAB

Congenital anomalies and MTCT can be linked in our minds with pregnancy exposures; other more common adverse pregnancy outcomes (SAB, SB, PTD, SGA and NND are often not linked overtly, and hence evoke less emotion / reaction

Longer-term child outcomes

Child health outcomes of possible concern	Outcome measures
• Bone: lower infant bone mineral content with maternal TDF *(PHACS/SMARTT);* LPV/r-ART compared with ZDV *(PROMISE)*	• Bone mineral density
• Neurodevelopment: ddI/d4T (ND disability); atazanavir, saquinavir (language delay); LPV/r (adaptive behavior), nelfinavir (cognitive), TDF (social-emotional) *(PHACS/SMARTT);* EFV (language) *(Tshipidi Plus)*	• Neurodevelopment, behavior
• ARV drug resistance in infected infants: nearly 100% with NNRTI resistance and ~3/4 with NRTI resistance, after exposure	• Drug resistance
• Cancer: increased incidence after 1st trimester ddI exposure *(French Perinatal)*	• Long-term follow-up for cancer

Clinical trials cannot answer questions about 1st TM exposure or rare events



- **Weeks 3 to 8 Post fertilization: embryogenesis/**period of major organ development (most sensitive to teratogens)
- Require post-marketing **surveillance / pharmacovigilance** to ascertain outcomes after drug **exposure from conception, or rare events** (clinical trials not feasible)

Many additional questions remain…

What characteristics should an ARV have, to be prioritized for study in PLW?

Not all drugs warrant a clinical trial

Prioritize drugs that are likely to be used by significant numbers of PLW and meet new need

How do we achieve effective messaging to PLW and their families, about findings from studies in PLW?

Confusion and mistrust if safety concerns arise in study of new drug in pregnancy

Need to be particularly thoughtful with design (e.g. rates of rare events such as congenital anomaly, stillbirth may vary by chance)

How can stakeholders – researchers, public health practitioners, community, industry, regulators – work together to optimize approach and effect change?

Summary of key points

- **Pregnant women deserve access to high quality evidence informing the use of drugs in pregnancy**
- Growing momentum with multiple stakeholders to gain consensus as to how to improve and accelerate collection of this evidence
- Approach will require
  - Facilitating an environment that promotes research on relevant ARVs in pregnancy
  - Performing pregnancy studies before licensure of new drug, often concomitant with or embedded in Phase III trials in non-pregnant individuals

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