Prevention of HIV in pregnant and lactating people

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Key messages

• Women experience overlapping risks for HIV and pregnancy and have need of effective prevention options, but historically have been excluded from pre-licensure trials because of safety concerns.

• A paradigm shift is underway, with a call to action to include pregnant and lactating people in pre-licensure trials using a new set of decision criteria.

• This change is an opportunity for the HPTN to address the evidence gaps in pregnancy safety data, to educate communities and support participants, and to build the evidence base for current and future products.
Women in sub-Saharan Africa have an unmet need for HIV prevention

What share of the population living with HIV are women?, 2020
Among those aged 15 years and older.

Source: UNAIDS (via World Bank)
Fertility rates are highest in high HIV burden settings

Total fertility rate by country or area, 2019

Live births per woman:
- 4 or more
- 2.1 to less than 4
- 1.5 to less than 2.1
- Less than 1.5
- No data

Source: United Nations Population Division, 2020
Pregnancy and post-partum period associated with increased risk for HIV

Suggests that biological changes during pregnancy and the postpartum period increase HIV susceptibility among women.

Source: Thomson, JID 2018
The majority of paediatric HIV infections are due to new mothers not receiving ART, dropping off ART, or becoming infected during breastfeeding.

Number of new HIV infections among children by source of infection, 2022

- **Pregnancy**
  - Did not receive ART: 47,000 (36%)
  - Dropped off ART: 7,000 (6%)
  - Mother newly infected: 16,000 (12%)
  - Started ART before the pregnancy: 20,000 (15%)

- **Breastfeeding**
  - Did not receive ART: 17,000 (13%)
  - Dropped off ART: 13,000 (10%)
  - Mother newly infected: 20,000 (15%)
  - Started ART during the pregnancy: 13,000 (10%)
  - Started ART late in the pregnancy: 20,000 (15%)

https://data.unicef.org/topic/hivaids/emtct/
Concerns about fetal exposure to medications during pregnancy

Timing of *In Utero* Drug Exposure and Fetal Risk of Birth Defect

Historically women of childbearing potential are under-represented in trials, are required to use contraception, and required to stop study product if they become pregnant.
Excluding pregnant women from trials shifts risk of harm

Without research, pregnant people
- May be given drugs in the **wrong dose**
- May be given drugs that carry **unacceptable risk**
- May be denied access to critically needed drugs

Source: Colbers, 2019; PHASES working group, 2020
A paradigm shift is underway

• Multiple stakeholders have voiced their concerns around the exclusion of pregnant women from pre- and post-registration drug trials and the associated harms and risks of these policies.

• Three major conceptual shifts that will facilitate the inclusion of pregnant women in research:

- **Vulnerable population** ⟷ **Complex population**
- **Protection from research** ⟷ **Protection through research**
- **Presumptive exclusion** ⟷ **Fair inclusion**
If the agent is efficacious in non-pregnant adults (viral load suppression) and adequate drug exposures are achieved in pregnancy, then efficacy can be assumed in pregnancy without additional trials.

If the agent is efficacious in non-pregnant adults (viral load suppression) and adequate drug exposures are achieved in pregnancy, efficacy for prevention of vertical transmission can be inferred.

All new agents must be studied in pregnant woman for pharmacokinetics/optimal dosing and short-term safety.

Dedicated pregnancy safety studies assessing pregnancy, birth and infant outcomes should be conducted for all new ARVs with expected broad use in pregnant women and women who may become pregnant.

There is no expectation to have meaningful clinical information about teratogenicity risk before registration; Large numbers of observations with exposure at conception/early pregnancy are needed to identify increased risk of rare events and will only come through active surveillance/Phase 4 studies.

Once pharmacokinetic/dosing and short-term safety in pregnancy are determined to be adequate, there should be no restrictions to access during pregnancy once the ARV is licensed.
A framework for accelerating inclusion in pre-licensure clinical trials

Trials of DVR, CAB, LEN, ISL all include pregnant and lactating people

Proposed steps for accelerating ethical inclusion of pregnant women in research:
- Earlier completion of non-clinical studies
- Pregnancy PK/safety for ALL NEW drugs
- Women becoming pregnant in trial can consent to stay on drug → PK/safety data (unless reason not to)
- Comprehensive strategic surveillance
- For PRIORITY drugs: dedicated pregnancy safety study during Phase 3 or early post-approval

WHO/IMPAACT, 2022
Congenital anomalies are not the only (nor even the most important) safety endpoint related to medications taken in pregnancy.

**Pregnancy outcomes, including**
- Preterm delivery (PTD, birth <37 weeks)
- Low birthweight (LBW, <2500g)
- Small for gestational age (SGA, <10th %ile)
- Fetal loss (miscarriage, stillbirth)

**Maternal health outcomes**

**Child outcomes**

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Slide courtesy S. Lockman
Congenital anomalies are not the only safety endpoint related to medications taken in pregnancy

Assessing pregnancy and neonatal outcomes in Malawi, South Africa, Uganda, and Zimbabwe: Results from a systematic chart review

<table>
<thead>
<tr>
<th>Place of delivery</th>
<th>Malawi N = 2442</th>
<th>Uganda N = 3835</th>
<th>South Africa N = 1936</th>
<th>Zimbabwe N = 2213</th>
<th>Overall N = 10426</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current health facility</td>
<td>2282 (93.4)</td>
<td>3607 (94.1)</td>
<td>1858 (96.0)</td>
<td>2032 (91.8)</td>
<td>9779 (93.8)</td>
</tr>
<tr>
<td>At a different health facility</td>
<td>131 (5.4)</td>
<td>180 (4.7)</td>
<td>26 (1.3)</td>
<td>71 (3.2)</td>
<td>408 (3.9)</td>
</tr>
<tr>
<td>At a home (private residence)</td>
<td>28 (1.1)</td>
<td>33 (0.9)</td>
<td>48 (2.5)</td>
<td>109 (4.9)</td>
<td>218 (2.1)</td>
</tr>
<tr>
<td>Not documented</td>
<td>1 (0.0)</td>
<td>15 (0.4)</td>
<td>4 (0.2)</td>
<td>1 (0.0)</td>
<td>21 (0.2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mode of delivery</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Vaginal delivery</td>
<td>1819 (74.5)</td>
<td>2726 (71.1)</td>
<td>1258 (65.0)</td>
<td>1819 (82.2)</td>
<td>7622 (73.1)</td>
</tr>
<tr>
<td>Cesarean delivery</td>
<td>592 (24.2)</td>
<td>1082 (28.2)</td>
<td>674 (34.8)</td>
<td>362 (16.4)</td>
<td>2710 (26.0)</td>
</tr>
<tr>
<td>Other</td>
<td>28 (1.1)</td>
<td>9 (0.2)</td>
<td>0 (0.0)</td>
<td>32 (1.4)</td>
<td>69 (0.7)</td>
</tr>
<tr>
<td>Not documented</td>
<td>3 (0.1)</td>
<td>18 (0.5)</td>
<td>4 (0.2)</td>
<td>0 (0.0)</td>
<td>25 (0.2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pregnancy outcome</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Full term live birth</td>
<td>2094 (85.7)</td>
<td>3192 (83.2)</td>
<td>1387 (71.6)</td>
<td>1775 (80.2)</td>
<td>8448 (81.0)</td>
</tr>
<tr>
<td>Premature live birth (&lt;37 weeks)</td>
<td>261 (10.7)</td>
<td>400 (10.4)</td>
<td>400 (20.7)</td>
<td>258 (11.7)</td>
<td>1319 (12.7)</td>
</tr>
<tr>
<td>Stillborn/intrauterine fetal demise (≥20 weeks)</td>
<td>75 (3.1)</td>
<td>152 (4.0)</td>
<td>64 (3.3)</td>
<td>122 (5.5)</td>
<td>413 (4.0)</td>
</tr>
<tr>
<td>Outcome not documented</td>
<td>12 (0.5)</td>
<td>91 (2.4)</td>
<td>85 (4.4)</td>
<td>58 (2.6)</td>
<td>246 (2.4)</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Birthweight (grams)²</th>
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</thead>
<tbody>
<tr>
<td>Low birthweight (&lt;2500 g)²</td>
<td>353 (15.1)</td>
<td>574 (15.9)</td>
<td>324 (17.4)</td>
<td>288 (13.8)</td>
<td>1539 (15.5)</td>
</tr>
<tr>
<td>Neonatal death²</td>
<td>61 (2.6)</td>
<td>42 (1.2)</td>
<td>24 (1.3)</td>
<td>65 (3.2)</td>
<td>192 (2.0)</td>
</tr>
</tbody>
</table>

1 Statistics are N (%) for categorical variables and mean ± SD (range) for continuous variables.
2 Birthweight reported for livebirths only.
3 Livebirths only. Missing data for N = 118 (1.2%) included in the denominator.

Pre-term birth complications are the leading cause of death among children under 5 years.

Pre-term neonates who survive are at greater risk of short and long-term morbidities.

LBW associated with worse health outcomes.
Pre-term birth and low-birth weight associated with negative outcomes

- **Pre-term birth**
  - Preterm birth complications = leading cause of death among children under 5 years (35% of deaths among neonates)
  - Pre-term neonates who survive has greater risk of short-term and long-term morbidities
  - Poor long-term outcomes including cognitive disability, impaired hearing/vision, neurological complications, infections, and chronic pulmonary, cardiovascular, metabolic, and renal disorders (especially in very preterm babies)
  - Associated with significant costs to the health system, and families

- Low-birth weight (or small for gestational age) babies are at significantly higher risk of poor health outcomes (including mortality), particularly in low-income settings

[https://www.who.int/news-room/fact-sheets/detail/preterm-birth](https://www.who.int/news-room/fact-sheets/detail/preterm-birth); Chawanpaiboon, 2019
## A need for harmonised safety outcomes

<table>
<thead>
<tr>
<th>Birth outcomes</th>
<th>Maternal health outcomes</th>
<th>Neonatal/infant outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stillbirth</td>
<td>Mortality (during pregnancy, L&amp;D)</td>
<td>Mortality (early neonatal)</td>
</tr>
<tr>
<td>Preterm birth (and whether spontaneous vs indicated)</td>
<td>Prolongation of hospitalization or re-hospitalization</td>
<td>Neonatal mortality (28 days)</td>
</tr>
<tr>
<td>Birthweight</td>
<td>Blood pressure, hypertensive disorders of pregnancy</td>
<td>Infant mortality (first year)</td>
</tr>
<tr>
<td>Small for gestational age (SGA) (&lt;10th percentile)</td>
<td>Weight gain in pregnancy</td>
<td>Growth (first year)</td>
</tr>
<tr>
<td>Major congenital anomaly (with neonatal surface exam and fetal anatomic ultrasound)</td>
<td>Caesarean section (with indication)</td>
<td>Congenital anomalies (6 months)</td>
</tr>
<tr>
<td>Early fetal loss/miscarriage</td>
<td>Gestational diabetes</td>
<td>Hospitalization (first year)</td>
</tr>
<tr>
<td></td>
<td>Pregnancy and labor/delivery complications</td>
<td>Liver, renal, full blood count (if breastfeeding, and dep. on drug)</td>
</tr>
<tr>
<td></td>
<td>Liver, neuropsychiatric, renal, bone toxicity (depending on drug)</td>
<td>Neurodevelopment</td>
</tr>
</tbody>
</table>

WHO Pregnancy and Therapeutics Work Group, 2023
Importance of a comparator group

- Very important to collect contemporary outcomes data in medication-unexposed comparator group in the same locations/populations

- Cautious use of “Background” rates from the most comparable population are a far less desirable alternative, if contemporaneous data from comparator group not feasible
HPTN 084 OLE key research questions

Safety
• Are the maternal, pregnancy and infant safety outcomes similar between CAB exposed vs. non-exposed, with active dosing in OLE?

Pharmacology
• Do we need dose adjustment during pregnancy?
  • PBPK model predictions suggest bimonthly long-acting cabotegravir is likely to maintain antiviral efficacy throughout pregnancy.

• What can we say about infant exposure to CAB during lactation?
  • Data on CAB in breastmilk limited
  • Data from DTG suggests low concentrations in breastmilk
    • median ratio of DTG in breast milk to maternal plasma was 0.03 (median 66.7 ng/mL
    • In DTG elimination by newborn infants is prolonged but no AEs have been reported
  • Additional virology questions

Atoyebi, CROI 2022; Waitt, PLoS Med 2019
FDA Warns of Birth Defects from HIV Drug Dolutegravir
— Safety signal seen in Botswana trial data

by John Gever, Managing Editor, MedPage Today   May 18, 2018

Dolutegravir (Tivicay, Triumeq, Juluca): signal of increased risk of neural tube defects; do not prescribe to women seeking to become pregnant; exclude pregnancy before initiation and advise use of effective contraception

New safety recommendations have been issued while an EU review evaluates cases of neural tube defects in babies born to mothers who became pregnant while taking the HIV medicine dolutegravir.

Over 3 million people on new HIV drug, but not all smooth sailing

A district perspective

Dr. Josephine Otchere-Darko, programme head of Wits RHI’s HIV/TB care and treatment programme in Ekurhuleni, says that initially there were mixed emotions and slow uptake, due to fears around the usage of TLD, particularly in pregnancy. Yet uptake started to increase a little after the studies that essentially “nullified the neural tube defect issue”.
Participants will accept relaxed contraceptive requirements: 92%
Participants will accept injections during pregnancy: 58%
You would accept injections during pregnancy: 51%
Participants accept injections during lactation: 70%
Partners will object to injections during pregnancy and lactation: 65%

N=101 participants, mainly community stakeholders

Emphasized safety concerns and need for information +++

Pregnant women part of social network with many stakeholders in a safe pregnancy outcome

White, JIAS in press
HPTN 084 design, OLE period

No LARC requirement

- CAB
  - TDF/FTC
  - CAB
  - CAB
  - TDF/FTC
  - Eligible sub-study
  - Eligible sub-study
  - Eligible sub-study
  - CAB
  - TDF/FTC

Follow through to 1 year post-partum

- No consent, follow as below
  - Continue follow up and assess outcomes
Progress to date

• Pregnancies during OLE
  • N=268
  • 161/207 eligible for substudy consented (79%)
    • Both prevalent and incident pregnancies
    • Participants starting CAB and those at steady state
  • Follow up ongoing
  • 44 participants have at least one post-partum visit

• Cumulatively since start of HPTN 084
  • 465 pregnancies, 394 CAB exposed, 71 no CAB exposure
  • 232 live births, 191 CAB exposed, 41 no CAB exposure
Key messages

• Women experience overlapping risks for HIV and pregnancy and have need of effective prevention options, but historically have been excluded from pre-licensure trials because of safety concerns

• A paradigm shift is underway, with a call to action to include pregnant and lactating people in pre-licensure trials using a new set of decision criteria

• This change is an opportunity for the HPTN to address the evidence gaps in pregnancy safety data, to educate communities and support participants, and to build the evidence base for current and future products
Sponsor
• U.S. National Institute of Allergy and Infectious Diseases (NIAID), all components of the U.S. National Institutes of Health (NIH)

Additional funding support
• ViiV Healthcare
• Bill & Melinda Gates Foundation
• National Institutes of Mental Health

Pharmaceutical support
• Gilead Sciences
• ViiV Healthcare

HIV Prevention Trials Network
• Leadership and Operations Centre, FHI360
• Laboratory Centre (Johns Hopkins)
• Statistical Center for HIV/AIDS Research and Prevention, Fred Hutchison Cancer Research Center
• HPTN Leadership

HPTN 084 Study team
• 20 sites in 7 countries in sub-Saharan Africa
• Community advisory boards and partners
• Pregnancy advisors: Friday Saidi, Lynda Stranix-Chibanda

… and our study participants!