HIV Treatment in Pregnancy

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No disclosures
Pregnant women are of central importance in global HIV treatment

Antiretrovirals in pregnancy and:

- Vertical transmission
- Pregnancy outcomes
- Congenital anomalies
- Mother’s health outcomes
- Child outcomes

Current pregnancy antiretroviral treatment (ART) recommendations

- Evidence gaps

Paradigm shift: consider all of these outcomes, and protect pregnant women through research
Pregnant women are central to our global approach to HIV treatment

- 51% of persons living with HIV globally are women\(^1\)

- \(~1.3\) million women with HIV are pregnant each year\(^1\)
  - Most women with HIV will be pregnant at least once following diagnosis

- Need pregnancy data to identify safest, most effective HIV treatment regimens for women and their children throughout their life course

- Pregnancy findings can affect HIV treatment of millions of individuals

\(^1\)UNAIDS 2020
HIV treatment in pregnancy and…

Vertical transmission (VT)

Pregnancy outcomes

Mother’s health outcomes

Child outcomes
Maternal combination ART dramatically reduces VT

20%-45% risk of VT if no intervention

<table>
<thead>
<tr>
<th>VT risk:</th>
<th>5-10%</th>
<th>10-15%</th>
<th>5-20%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy</td>
<td>36.7%</td>
<td>16.5%</td>
<td>13.1%</td>
</tr>
<tr>
<td>Labor and Delivery</td>
<td>6.5%</td>
<td>3.7%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Breastfeeding</td>
<td>1.1%</td>
<td></td>
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</tr>
</tbody>
</table>

- None 100% BF
- Short ZDV 100% BF
- SD NVP 100% BF
- Short ZDV+sdNVP 50% BF Cote
- Short ZDV+sdNVP 50% BF Bots
- Short ZDV+sdNVP NO BF, Thai.
- ART, 100% BF Botswana

% vertical transmission
Transmission is very low with viral suppression on ART from early in pregnancy

8075 mothers on ART and their non-breastfed infants, 2000-2011, French Perinatal Cohort

<table>
<thead>
<tr>
<th>Timing of ART start</th>
<th>Vertical Transmission, %</th>
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<tbody>
<tr>
<td>Before conception</td>
<td>0</td>
</tr>
<tr>
<td>1st trimester</td>
<td>0.3%</td>
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<tr>
<td>2nd trimester</td>
<td>0.2%</td>
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<tr>
<td>3rd trimester</td>
<td>0.3%</td>
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<td></td>
<td>0.5%</td>
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<td></td>
<td>0.9%</td>
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<td>3%</td>
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<td>4.4%</td>
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HIV RNA at delivery (copies/mL)
- <50
- 50-400
- >400

- Earlier ART start = better (lowest transmission with pre-conception ART)
- Maternal HIV-1 RNA = independent predictor of vertical transmission
- U likely = U with ART from conception, viral suppression, no breastfeeding
Does ART regimen affect vertical transmission?

DTG reduces viral load more rapidly in pregnancy than EFV (Kintu Lancet HIV 2020; Chinula AIDS 2020)

Meta-analysis: 5 trials of DTG/XTC/TDF (or TAF) vs. EFV/XTC/TDF (n=1,074)

- Delivery VL suppression: DTG (90%) > EFV (72%), p=0.001
- 5 cases VT: all in DTG arms (5/659, 1%)

Similar VT at birth with DTG/FTC/TDF (n=999) and EFV/FTC/TDF (n=883) started in pregnancy, Botswana

Asif AIDS 2020 Conference

Although VL drops more quickly with DTG, both DTG- and EFV-ART are very effective at preventing vertical transmission.
How well are we doing with preventing VT globally?

% of pregnant women on ART and new pediatric infections in focus countries, 2019

In 2019:
- 85% ART in pregnancy
- >50% conceived on ART
- BUT, still ~150,000 new pediatric infections
Primary reasons for new HIV infections in children, 2019

THE THREE PRIMARY MISSED OPPORTUNITIES FOR PREVENTING VERTICAL TRANSMISSION:

1. Mother did not receive ART (pregnancy > breastfeeding)
2. Incident HIV infection (breastfeeding > pregnancy)
3. Dropped off ART (breastfeeding > pregnancy)

Focus countries 2019, UNAIDS 2020
Key points, vertical transmission

1. Viral suppression on maternal ART from early pregnancy can nearly eliminate VT through delivery, and rate as low as 1% possible even with breastfeeding

   Lowest transmission with pre-conception ART

2. Work to do: increase ART coverage and maternal HIV re-testing (to diagnose incident HIV); reduce HIV incidence; and better support retention in care and ART adherence
HIV treatment in pregnancy and...

Vertical transmission

**Pregnancy outcomes**
- Preterm delivery (PTD, birth <37 weeks)
- Low birthweight (LBW, <2500g)
- Small for gestational age (SGA, <10th percentile)
- Stillbirth
- Neonatal Death

Mother’s health outcomes

Child outcomes

Vertical transmission and congenital anomalies

Other outcomes
Why are preterm birth and low birthweight so important?

- Preterm birth = the leading cause of neonatal and under-5 mortality globally
  - Poor long-term outcomes, especially in very preterm babies

- Low birthweight (or small for gestational age) babies are at significantly higher risk of dying, particularly in low-income settings
Pre-ART era: women with HIV had much higher rates of adverse pregnancy outcomes than women without HIV

Better outcomes with ART in pregnancy than without ART ...but not a free ride

Adverse Birth Outcomes, Antiretroviral Naïve Women 1980-2014

Wedi et. al., Lancet Infect Dis, 2016
Worse pregnancy outcomes with 3-drug ART than with ZDV

PROMISE TRIAL (IMPAACT P1077)

Women enrolled with CD4 $>350$ cells/mm$^3$ and no AIDS illness

Fowler NEJM 2016
Rates of adverse pregnancy outcomes differ by maternal ART regimen

**BOTSWANA TSEPAMO SURVEILLANCE STUDY**

**EFV/FTC/TDF: LOWEST**

Adverse pregnancy outcomes compared with other ART

LOWER adverse pregnancy outcomes still observed in **HIV-negative women** than women with HIV on ART

<table>
<thead>
<tr>
<th>ART Regimen</th>
<th>Any Outcome</th>
<th>Severe Outcome</th>
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<tbody>
<tr>
<td>HIV-unexposed (N=34,616)</td>
<td>29%</td>
<td>10%</td>
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<tr>
<td>TDF/FTC/EFV (N=2,503)</td>
<td>36%</td>
<td>12%</td>
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<tr>
<td>TDF/FTC/NVP (N=775)</td>
<td>42%</td>
<td>18%</td>
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<tr>
<td>ZDV/3TC/NVP (N=1,403)</td>
<td>47%</td>
<td>21%</td>
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<tr>
<td>TDF/FTC/LPV-r (N=237)</td>
<td>48%</td>
<td>20%</td>
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<tr>
<td>ZDV/3TC/LPV-r (N=169)</td>
<td>45%</td>
<td>23%</td>
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</table>

6% STILLBIRTH

Comparisons of all regimens to TDF/FTC/EFV were statistically significant

Adjusted for age, education, and gravida

Zash JAMA Pediatrics 2017; slide adapted from Zash

LOWER adverse pregnancy outcomes still observed in **HIV-negative women** than women with HIV on ART

Rates of adverse pregnancy outcomes differ by maternal ART regimen

Comparisons of all regimens to TDF/FTC/EFV were statistically significant

Any adverse pregnancy outcome

Severe adverse pregnancy outcome
What about pregnancy outcomes with more contemporary maternal ART regimens?

VESTED TRIAL (IMPAACT 2010)
Conception on ART and pregnancy outcomes

- Conceiving on some regimens *may* (?) be associated with worse pregnancy outcomes
- Advantages of uninterrupted maternal ART outweigh possible risks

**Meta-analysis: ART start pre-conception vs. in pregnancy**

**PROMISE (IMPAACT P1077), 2nd Pregnancy**

- Spontaneous abortion
  - Conceived on ART: 17%
  - Did not conceive on ART: 15%
- Stillbirth
  - Conceived on ART: 5.2%
  - Did not conceive on ART: 0.9%

**Risk ratio (95% CI)**

- Very preterm delivery
  - 1.80 (1.27-2.57)
  - 1.41 (1.13-1.77)
  - 1.53 (1.22-1.93)

- Low birthweight
  - 1.21 (0.97-1.51)
  - 1.57 (1.04-2.37)
  - 1.30 (1.04-1.62)

**PROMISE (IMPAACT P1077)**

- ITT 2.0 (1.1-3.5)
- (as-treated 1.4 [0.8-2.4])

*Uthman Lancet HIV 2017*

*Hoffman CID 2019*
Higher prevalence of placental maternal vascular malperfusion with ART from conception

- ART before conception → 2-fold higher placental MVM
- MVM was significantly associated with preterm delivery and LBW

125 out of 130 participants took EFV-based ART
Key points, ART and pregnancy outcomes

1. Pregnancy outcomes are worse in women with HIV, even on ART
   But better outcomes on ART than untreated HIV

2. Pregnancy outcomes differ significantly by ART regimen

3. Common adverse pregnancy outcomes (preterm, small for gestational age) are major causes of child morbidity/mortality
   Gather and incorporate data for these outcomes in decisions
HIV treatment in pregnancy and...

Vertical transmission

Pregnancy outcomes

Congenital anomalies

Mother’s health outcomes

Child outcomes
Critical and sensitive periods in human development

Neural tube closes within 4 weeks of conception

<table>
<thead>
<tr>
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<th>PERIOD OF THE EMBRYO</th>
<th>PERIOD OF THE FETUS</th>
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<tr>
<td>WEEKS 1-2</td>
<td>3 4 5 6 7 8</td>
<td>12 16 20-36 38</td>
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</table>

- **3** TYPICALLY WHEN A WOMAN FIRST LEARNS SHE IS PREGNANT

**BRAIN/SPINAL CORD (CENTRAL NERVOUS SYSTEM)**
- **HEART**
- **ARMS / LEGS**
- **EARS**
- **EYES**

**MAJOR STRUCTURAL DEFECTS** can occur.

**TEETH**

**PALATE**

**EXTERNAL GENITALS**

**Weeks 3-8 post-fertilization:** embryogenesis → major organ development, most sensitive to teratogens
Antiretroviral pregnancy registry (APR): congenital anomalies with 1st trimester exposure

Summary of birth defects with 1st trimester exposures, prospective registry Jan 1989 – July 2020

- ~200 1st TM exposures to detect 2-fold increase in any anomaly (~3%)
- ~2,000 to detect 3-fold increase in rare anomaly like NTD (0.1%)
- 22 ARVs have enough data to detect a 2-fold increase in anomalies
- Only ddI and nelfinavir have elevated anomaly prevalence (no pattern)

http://www.apregistry.com/
## Preconception DTG and neural tube defects

<table>
<thead>
<tr>
<th>Studies with greater than 50 pre-conception DTG exposures</th>
<th># NTD / # Exposures, % prevalence</th>
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</thead>
<tbody>
<tr>
<td>Tsepamo Botswana (Zash AIDS 2020 Conf.)</td>
<td>7 / 3,591 (0.19%)</td>
</tr>
<tr>
<td>Brazil retrospective cohort (Pereira Lancet HIV 2021)</td>
<td>0-2 / ~1,084 (0 - 0.18%)</td>
</tr>
<tr>
<td>APR July 2020</td>
<td>1/479 (0.21%)</td>
</tr>
<tr>
<td>CDC/MoH Botswana (Raesima NEJM 2019)</td>
<td>1 / 152 (0.66%)</td>
</tr>
<tr>
<td>European DOLOMITE/EPPICC (Thorne Workshop on HIV &amp; Women 2020)</td>
<td>0 / 280* (0%)</td>
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</table>

At least 9 other studies, each with fewer than 100 women

**NTD prevalence in general population:** 0.06% - 0.1% (depending on folate fortification)

*One pregnancy termination of fetus with neuronal migration disorder and severe microcephaly*
Key points, congenital anomalies

1. True teratogens are very rare

2. Need prospective surveillance with large denominators to evaluate for rare events (particularly with preconception exposures)

3. Provide relevant pregnancy data to women to support their informed decisions
HIV treatment in pregnancy and...

Vertical transmission

Pregnancy outcomes

Mother’s health

Child outcomes
Physiological changes in pregnancy can alter drug pharmacokinetics (PK)

**Absorption**
- Nausea/vomiting
- Prolonged gastric transit time
- Higher intestinal pH

**Distribution**
- Higher blood volume (hemodilution)
- Decreased serum albumin (free drug)
- More body fat
- Different transporter expression

**Elimination**
- Higher cardiac output
- Increased renal blood flow/GFR

**Metabolism**
Activity of drug-metabolizing enzymes (mostly increase)

✧ Drug levels often (but not always) lower in late pregnancy (efficacy)
✧ Placental and breast milk transfer varies by drug
**Summary: pregnancy pharmacokinetics for current ARVs**

- **Good news!** despite lower pregnancy levels with most HIV drugs, usually sufficient to maintain efficacy
- **BUT** must evaluate pregnancy PK, because occasionally levels inadequate (e.g. cobicistat)

<table>
<thead>
<tr>
<th>NRTIs</th>
<th>NNRTIs</th>
<th>INSTIs</th>
<th>Entry inhibitors</th>
<th>Long-acting agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir</td>
<td>Doravirine</td>
<td>Bictegravir</td>
<td>Fostemsavir</td>
<td>CAB LA</td>
</tr>
<tr>
<td>Emtricitabine/lamivudine</td>
<td>Efavirenz</td>
<td>Dolutegravir</td>
<td>Ibalizumab</td>
<td>Rilpivirine LA</td>
</tr>
<tr>
<td>Tenofovir AF</td>
<td>Etravirine</td>
<td>Elviteg./cobi</td>
<td>Maraviroc</td>
<td>Islatravir</td>
</tr>
<tr>
<td>Tenofovir DF</td>
<td>Nevirapine</td>
<td>Raltegravir</td>
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<td></td>
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<tr>
<td>Zidovudine</td>
<td>Rilpivirine</td>
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</table>

**PIs**

- Atazanavir/r
- Darunavir/r
- Lopinavir/r

**Boosters**

- Cobicistat
- Ritonavir

**Entry inhibitors**

- Fostemsavir
- Ibalizumab
- Maraviroc

**Long-acting agents**

- CAB LA
- Rilpivirine LA
- Islatravir

*Clinicalinfo.hiv.gov*
ART in pregnancy and maternal health outcomes

Previously: maternal HIV drug resistance with short-course (1-2-drug) ARV

Rarely: virologic failure on ART due to lower plasma drug levels in pregnancy (e.g. cobicistat-boosted regimens)

Infrequently: adverse effects may differ in pregnancy/postpartum

- Weight gain (DTG, TAF)
- Gestational diabetes (unexpectedly: lower with DTG- vs EFV-ART in 1 study) (Mmasa, HIV Medicine 2021)
- Hypertensive disorders of pregnancy (NVP, Zash 2018; DTG at conception, Zash CROI 2021 Abstract 1302; ART initiation in pregnancy, Chadwick CROI 2021 Abstract 575; PIs and pre-eclampsia Conner CROI 2021 Abstract 578)
- Gastrointestinal intolerance (LPV/r) Cohan 2015
- Hepatitis (NVP) Renet J Ob/Gyn Canada 2013
- ? Postpartum suicidal ideation (EFV) Jones AIDS Behav 2020
ART in pregnancy and maternal health outcomes

Maternal pre-pregnancy BMI and pregnancy weight gain

- Low maternal weight → low birthweight, small for gestational age, preterm
- High maternal weight → macrosomia, Cesarean delivery, hypertension, diabetes
ART and weight gain in non-pregnant women

Integrase inhibitors and TAF → excess weight gain (particularly in women w/ INSTIs)

ADVANCE trial weight: women

- +12.3 kg TAF/FTC+DTG
- +7.4 kg TDF/FTC+DRG
- +5.5 kg TDF/FTC/EFV

Venter AIDS 2020, Abstract OAXLB0104
Antepartum weight gain differs by ART regimen started in pregnancy

**Botswana Tsepamo, Observational:**
- ART initiated 1-17 weeks gestation

**Recommended IOM weight gain 2nd/3rd trimesters (0.42 kg/week)**
- EFV/FTC/TDF: 0.31
- DTG+FTC/TDF: 0.35
- HIV-negative women: 0.44

**VESTED (IMPAACT 2010) RCT**
- ART initiated 14-28 weeks gestation

**Recommended IOM weight gain 2nd/3rd trimesters (0.42 kg/week)**
- EFV/FTC/TDF: 0.291
- DTG+FTC/TDF: 0.319
- DTG+FTC/TAF: 0.378

All between-group comparisons statistically significant except EFV vs DTG+FTC/TDF arms, IMPAACT 2010

Chinula CROI 2020 130LB

*Caniglia, eClin Med, 2020*

In both studies: lower-than-recommended weight gain occurred more frequently in women starting EFV/FTC/TDF
Weight in pregnancy & adverse outcomes, CROI 2021

VESTED (IMPAACT 2010)

CROI Hoffman #176

DTG vs EFV, TAF vs TDF started in pregnancy (RCT)

- Low weight gain pregnancy: higher risk adverse pregnancy outcomes
- Weight gain \( \rightarrow \) lower risk

TSEPMAMO

CROI Zash #571

DTG- and EFV-ART pre-conception (observational)

- Low (<50kg) baseline pregnancy weight: severe adverse pregnancy outcomes
- High (>90kg) baseline pregnancy weight: macrosomia, maternal hypertension

ADVANCE

CROI Baxevanidi #572

DTG vs EFV, TAF vs TDF preconception (projected)

- Pre-pregnancy obesity in women on DTG+F/TAF >144 weeks predicted to lead to more pregnancy complications seen with obesity
Gestational diabetes with DTG- vs. EFV-based ART in pregnancy

Women taking DTG-based ART were significantly less likely to have gestational diabetes (by OGTT) than women taking EFV-based ART.

Adjusted odds ratio 0.34 (95% CI 0.12-0.97)*

*Adjusted for age, BMI, gravidity, CD4, and whether ART started prior to or during pregnancy.
Key points, ART and maternal health

1. Pregnancy weight gain differs by ART regimen

2. Lower-than-recommended and higher-than-recommended pre-pregnancy weight (and pregnancy weight gain) can adversely affect different pregnancy outcomes
   - Greater pregnancy weight gain may be protective in some women
   - Unknown: implications over longer term, with subsequent pregnancies, and in different populations

3. Important to gather high-quality data on clinical endpoints with different ART regimens
HIV treatment in pregnancy and...

Vertical transmission

Pregnancy outcomes and neonatal death

Mother’s health outcomes

Child outcomes
HIV-exposed, uninfected (HEU) children

- 15 million HEU children
- HEU children have higher morbidity & mortality in LMIC
- Outcomes improved by breastfeeding (where recommended) and by ART in pregnancy *Arikawa CID 2018*
- Important to understand long-term impacts of HIV- and ARV-exposure

Number of children HIV exposed and uninfected globally, 2000-2018

Source: UNAIDS 2019 estimates

See CROI 2021 Van Lettow Abstract 585
Neonatal/infant mortality *may* vary by maternal ARV regimen.

**PROMISE:**
Infant mortality through week 1

- ZDV: 3.2%
- ZDV/3TC + LPV/r: 0.6%
- TDF/FTC + LPV/r: 4.4%

**IMPAACT 2010 / VESTED:**
Infant mortality through week 50

- DTG+FTC/TAF: 1.0%
- DTG+FTC/TDF: 2%
- EFV/FTC/TDF: 6.9%

*Period 1 of study*
ART in pregnancy and child growth and neurodevelopment

Research gaps: outcomes in older children and with newer antiretrovirals

See Jao #590 and Sirajee #592
Outline

Why are pregnant women a critical group of persons with HIV and not a niche population?

What we know about antiretroviral regimens in pregnancy and
  - Vertical transmission
  - Pregnancy outcomes
  - Mother’s health outcomes
  - Child outcomes

Current pregnancy antiretroviral recommendations and evidence gaps
## Antiretrovirals used in treating adults, 2020

<table>
<thead>
<tr>
<th>NRTIs</th>
<th>NNRTIs</th>
<th>INTEGRASE INHIBITORS</th>
<th>ENTRY INHIBITORS</th>
<th>PROTEASE INHIBITORS</th>
<th>CCR5 BLOCKER</th>
<th>LONG-ACTING AGENTS</th>
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</thead>
<tbody>
<tr>
<td>TAF (tenofovir alafenamide fumarate)</td>
<td>DOR (doravirine)</td>
<td>BIC (bictegravir)</td>
<td>Ibalizumab</td>
<td>DRV/r (darunavir/ritonavir)</td>
<td>MVC (maraviroc)</td>
<td>CAB LA (cabotegravir)</td>
</tr>
<tr>
<td>FTC (emtricitibine), 3TC lamivudine)</td>
<td>EFV (efavirenz)</td>
<td>DTG (dolutegravir)</td>
<td>Fostemsavir</td>
<td>ATV/r (atazanavir/ritonavir)</td>
<td></td>
<td>RIL LA (rilpivirine)</td>
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<tr>
<td>ABC (abacavir)</td>
<td>RPV (rilpivirine)</td>
<td>RAL (raltegravir)</td>
<td></td>
<td>TDF (tenofovir disoproxil fumarate)</td>
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<tr>
<td>TDF (tenofovir disoproxil fumarate)</td>
<td>ETR (etravirine)</td>
<td>ELV/c (elvitegravir/cobicistat)</td>
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<td>ZDV (zidovudine)</td>
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<tr>
<td>ZDV (zidovudine)</td>
<td>NVP (nevirapine)</td>
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# ARVs for pregnant women, US DHHS 2020

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<tbody>
<tr>
<td>TAF (alternative)</td>
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<td>FTC, 3TC</td>
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<tr>
<td>ABC</td>
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<td>ZDV (alternative)</td>
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<tr>
<th><strong>INTEGRASE INHIBITORS</strong></th>
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<td>BIC</td>
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<td>DTG</td>
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<td>RAL</td>
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<tr>
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<td>LPV/r</td>
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<td>CCR5 BLOCKER</td>
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<td>MVC</td>
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<tr>
<td>CAB LA</td>
<td>Insufficient data</td>
</tr>
<tr>
<td>RIL LA</td>
<td>Insufficient data</td>
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Also: insufficient data for 2-drug treatment in pregnancy (e.g. DTG/3TC, CAB/RIL)  
See CROI 2021 Abstract Mandelbrot 570
## Guidelines: preferred antiretrovirals during pregnancy

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<th>PIs</th>
<th>NNRTIs</th>
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<tbody>
<tr>
<td>DHHS and EACS</td>
<td>TDF/XTC or ABC/3TC</td>
<td>+</td>
<td>DTG or RAL BID</td>
<td>OR DRV/r or ATV/r <em>(DHHS)</em></td>
</tr>
<tr>
<td>WHO</td>
<td>TDF/3TC</td>
<td>+</td>
<td>DTG</td>
<td>OR EFV 400</td>
</tr>
</tbody>
</table>

### If conceive on ART with HIV-1 RNA suppression: generally continue regimen

*consider switch if on cobicistat-boosted regimen; recommend switch if on d4T, ddI, FPV, IDV, NFV, SQV, TPV, two-drug ART, triple-NRTI*

A woman-centered approach in which the woman “…receives full information about risks and benefits…and is supported in making voluntary choices around medical therapy…”
Newer HIV treatment/prevention agents, and current phase of study

Phase IIa / IIb

- Leronlimab (MAb)
- Islatravir LA (PrEP; soon Ph III)
- Islatravir LA (+MK-8507)
- ABX464 (rev inh)
- 3BNC117 (BNAb)
- GSK 3640254 (matur inh)
- GS-6207 (capsid inh)
- Albuvirtide (fusion inh)

Phase III

- Cabotegravir LA
- UB-421 (anti-CD4 rec)
- Islatravir (ISL/DOR)
- VRC01[LS] (BNAb)
- Lenacapavir
- Dapivirine ring

Phase IV

- Tenofovir Alafenamide
- Bictegravir
- Doravirine
- Ibalizumab
- Fostemsavir
- Cabotegravir/Rilpivirine LA

Adapted with permission from slide prepared by C Thorne/A Pozniak
Newer HIV agents: plans for study in pregnancy?

- **Long-acting CAB, RIL, ISL, LEN**: if become pregnant in clinical trial can consent to stay on drug (PK, safety data)
- **DOR, BIC, TAF, LA CAB**: “opportunistic” studies in routine care (IMPAACT 2026, PANNA networks, others)
- **Dapivirine ring**: DELIVER randomized trials in pregnant (NCT03965923) and breastfeeding (NCT04140266) women

**Phase Ila / Ilb**
- Leronlimab (MAb)
- Islatravir LA (PrEP; soon Ph III)
- Islatravir LA (+MK-8507)
- ABX464 (rev inh)
- 3BNC117 (BNAb)
- GSK 3640254 (matur inh)
- GS-6207 (capsid inh)
- Albuvirtide (fusion inh)

**Phase III**
- Cabotegravir LA
- UB-421 (anti-CD4 rec)
- Islatravir (ISL/DOR) & ISL
- VRC01[LS] (BNAb)
- Lenacapavir
- Dapivirine ring

**Phase IV**
- Tenofovir Alafenamide
- Bictegravir
- Doravirine
- Ibalizumab
- Fostemsavir
- Cabotegravir/Rilpivirine LA
Long-acting agents for HIV prevention and treatment

- Important drugs! Potentially useful postpartum
- Even if stop 1st TM, drug present through delivery
- Almost no human pregnancy/lactation data

Cabotegravir in pregnancy:
- PK 3 women conceiving on CAB LA (stopped drug): rate of decline in expected range for non-pregnant (Patel CROI 2020)
- Low placental transfer of CAB ex vivo (Pencole AIDS 2020)
Outline

Why are pregnant women a critical group of persons with HIV and not a niche population?

What we know about antiretroviral regimens in pregnancy and
- Vertical transmission
- Pregnancy outcomes
- Mother’s health outcomes
- Child outcomes

Current pregnancy antiretroviral recommendations and evidence gaps
Generally poor track record for studying drugs in pregnancy

“During trials, participants have close monitoring...why leave pregnant women to experiment with drugs but without adequate follow-up?”
How do we improve upon the status quo?

Conceptual shifts that will facilitate inclusion of pregnant women in research

- **Vulnerable population** → **Complex population**
- **Protection from research** → **Protection through research**
- **Presumptive exclusion** → **Fair inclusion**

*The PHASES Working Group, call to action, 2020*
A call to include pregnant women in research

Gathering momentum for change: numerous initiatives, e.g.

U.S. Task Force on Research Specific to Pregnant & Lactating Women (PRGLAC)

FDA draft guidance, Second Wave Initiative, PHASES Project, and many others globally

IMPAACT and WHO: advancing research on HIV drugs during pregnancy/lactation
WHO & IMPAACT Dec 2019: advancing pharmacology studies in pregnant and lactating women

**Figure 1** Proposed approach to pharmacokinetic studies of ARVs during pregnancy and the postpartum period

First small full PK studies During phase II/III
- Full PK curve 2nd trim
- Full PK curve 3rd trim
- Cord/washout samples neonate
- Full PK curve > 6 weeks Post partum (w/ milk if lactating)

**Small sample size (16-24)**
- Intensive sampling
- Intra-subject comparison
- Compare to PK non-pregnant women

Follow up sparse sampling studies POP PK
- X X X X X
- X X X

**Larger (heterogenous) sample size**
- Sparse sampling
- Intra-subject comparison and/or
- Compare to PK non-pregnant women
- Perform covariate analysis

**Fig. 2. Investigation stage for new antiretroviral drugs as of June 2019.**

(CI: capsid inhibitor; M1: maturation inhibitor; A1: attachment inhibitor; F1: fusion inhibitor; R1: reverse transcriptase抑制剂; LA: long acting; QD: once daily; BID: twice daily; red: PrEP and HIV treatment; blue: PrEP only; black: HIV treatment only; black: HIV treatment resistant virus.)

Clinical Trial Drug Development Phases, with focus on drugs that will be used in pregnancy.

**New drugs**
- Combinevir (GSK3732354)
- GS-CA1 (CI, LA)
- GS-5207/GS-CA2 (CI, LA)
- GS-5640254 (M1, QD)
- GS-9131 (NRTI, QD)
- Abacavir (CI, LA)
- PRe 32 (LAM, LVD, NA)
- Dapivirine (NNRTI, QD)
- Cabotegravir (INSTI, LA)
- Bictegravir (INSTI, QD)
- Efavirenz/Epipip (NNRTI, QD)
- Maraviroc (CCR5, QD)
- TAF/FTC (NRTI, QD)

**Approaches to optimize and accelerate pharmacology studies in pregnant and lactating women**

Meeting Report 13-14 June 2019
Washington, DC, USA
WHO & IMPAACT 2020 - now

Workshop Part 1

Welcome to the Virtual Workshop on Approaches to Enhance and Accelerate Study of New Drugs for HIV and Associated Infections in Pregnant Women

DECEMBER 8-10, 2020

Workgroups

Non-clinical

Trials in pregnant women

Study design

Surveillance

Advocacy

Workshop Part 2

SAVE THE DATES!!

Virtual Workshop on "Approaches to Enhance and Accelerate Study of New Drugs for HIV and Associated Infections in Pregnant Women" (Part 2)

6 & 7 July 2021
Potential ways to increase the inclusion of pregnant women in research

Steps under consideration for accelerating ethical inclusion of pregnant women in research:

- Earlier completion of non-clinical studies
- Women becoming pregnant in trial can consent to stay on drug → PK/safety data (unless reason not to)
- For high-priority drugs: dedicated pregnancy PK +/- larger safety study during Phase III or early post-approval
In conclusion
Key points

Optimizing care of pregnant women is central to our global approach to HIV treatment.

We know how to prevent vertical transmission, BUT implementation gaps remain AND antiretroviral regimen can affect multiple pregnancy, maternal and child health outcomes.

  Need to holistically understand and incorporate all of these outcomes in our care.

Women deserve high-quality evidence for medications that they will use throughout their lifecourse, including during pregnancy and lactation.
Thank you!

For listening, & to the many women who take part in this research

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