Pediatric Workshop & IAS 2019
Selected PMTCT, Pediatric, Adolescent, and Maternal/Adult Abstracts

Lynne M. Mofenson MD

Large set: 08/05/2019
UNAIDS/WHO Update on Pediatric HIV 2018
New Infections in Children

63% Decline New Infections Since 2000 – But Progress Has Stalled

Mahy M et al. Pediatric HIV Workshop, July 2019, Mexico City

Number of New Child Infections, Globally, 2000-2018

Only 8% decline past 2 years

160,000 in 2018

2018 target: 40,000

Source: UNAIDS 2019 estimates and Global AIDS Monitoring 2019
Number of Children 0-14 Years Living with HIV by Age

1.7 Million Children Living with HIV in 2018

Mahy M et al. Pediatric HIV Workshop, July 2019, Mexico City

Growing proportion of children in the older age group 10-14 years

Source: UNAIDS 2019 estimates and Global AIDS Monitoring 2019
Promising Declines in New Infections Among Young Women
But Still Considerably Higher than Young Men

Hadler S. IAS, July 2019, Mexico City

New HIV Infections among young women and young men, 23 focus countries, 2010-2018

Source: UNAIDS 2019 estimates.
AIDS-Related Pediatric Mortality

AIDS-Related Deaths Has Declined in Children – But Not Among Adolescents

Mahy M et al.  Pediatric HIV Workshop, July 2019, Mexico City

Source: UNAIDS 2019 estimates and Global AIDS Monitoring 2019

Decline in pediatric AIDS-related mortality has slowed

No real decline in AIDS-related mortality in adolescents 15-19 years

→ Decline in pediatric AIDS-related mortality has slowed

→ No real decline in AIDS-related mortality in adolescents 15-19 years
Global ART Coverage for Children

54% of HIV+ Children Are Receiving ART in 2018 – With Large Geographic Variation

Mahy M et al. Pediatric HIV Workshop, July 2019, Mexico City

Global ART coverage:

- 54% among children
- High variation globally, very low coverage in West-Central Africa
- 62% among adults
- 82% among pregnant women

Source: UNAIDS 2019 estimates and Global AIDS Monitoring 2019
Scale-Up of Treatment for Children is Slowing:
New, Innovative Modalities to Identify Children with HIV are Needed

Hadler S. IAS July 2019, Mexico City

Number of children receiving ART and targets, global and 23 focus countries 2010-2018

Failure to meet 2018 target of 1.6M children on ART
Way off lowered target for ART in 1.4 M children by 2020

Source: Global AIDS Monitoring, 2019
Treatment Cascade for Children

In Children Receiving ART, Viral Suppression Remains Suboptimal

Mahy M et al. Pediatric HIV Workshop, July 2019, Mexico City

Percentage of children living with HIV who are diagnosed, receiving ART and have suppressed viral load, and PHIA results countries with available data, 2018

Viral suppression in children on ART ranges from ~25% to 65% (supported by PHIA data)

6/11 countries have viral suppression rates in children on ART of <50%

Source: UNAIDS 2019 estimates and Global AIDS Monitoring 2019
Increasing Proportion of HIV-Exposed but Uninfected
As of 2018, Roughly 1.5 Million HEU Children – Increasing Proportion HIV/ART-Exposed

Mahy M et al. Pediatric HIV Workshop, July 2019, Mexico City

Importance of assuring children are not just free of HIV but are surviving without adverse consequences of HIV/ART exposure

Source: UNAIDS 2019 estimates and Global AIDS Monitoring 2019
- Cross-sectional, two-stage, cluster sample to obtain nationally representative household surveys to assess HIV epidemic (~30,000 participants including 5,000-10,000 children <15 yr)
- 1/3-1/2 surveys randomly selected to include children
- Population: Last-born child of women who reported being pregnant in preceding 3 yr; pregnancies in 2012-2018

**HIV in Children < 14 Yrs General Population, 2016-2018**

- Pooled *population* prevalence: 0.7% (95% CI: 0.6%-0.8%)
- Total estimated number: 570,000 (95% CI 380,000-760,000)

**Infants 0-17 Mos Born to HIV+ Mothers (N=440), 2016-2018, 6 Countries**

- Pooled prevalence: 9.0% (95% CI: 5.6%-12.3%)

Overall MTCT rate *still* suboptimal in 2016-2018 - consistent with slowing progress
Viral Load Suppression (VLS) <1,000 c/mL Children and Adults in PHIA's

Saito S. Pediatric HIV Workshop, July 2019, Mexico City

VLS in HIV+ Children < 14 Yr, 2016-2018, 10 countries

→ Pooled % VLS only 37% (95% CI 31-43%)

VLS in Children < 14 Yr vs Adults 15-49 Yr, 2016-2018, 10 countries

→ Pooled % VLS children: 37%
→ Pooled % VLS adults: 57%

Why is pediatric VLS so poor?
→ Lack of potent ARVs for children?
  • Delays obtaining appropriate dosing?
  • Delay in transitioning to better drugs?
→ Lack of appropriate formulations for young children?
→ Dependent on adult administration?
→ Drug resistance?
Mozambique: Community HIV Prevalence and Factors Associated with Mortality, HIV-Exposed Children Age <4 Years

Fuente-Soro L et al. IAS July 2019, Mexico City Abs. MOPEC323

- Oct 2017-April 2018 cross-sectional household survey, southern Mozambique; households with live births in prior 4 years randomly selected.

- Of 3,487 mother/child pairs included, maternal HIV prevalence 27.7% (n=965).

- Of 965 HIV-exposed children, 49 (5.1%) HIV+, 851 HIV-, 65 (6.7%) unknown status.

- 33 child deaths; mortality 30.8 deaths/1000 live births in 48 mo prior to survey

→ Cumulative mortality in children was ↑ in those with mother dead or not located in the household due to migration or absence.

→ Only 16% of HIV+ children who died were on ART (53% of HIV+ children on ART)

→ Children with unknown status similar mortality as HIV+
PHIA 2015-2017: Progress in Health Outcomes in Children Born to Women with HIV, 8 Countries

Saito S et al. IAS July 2019, Mexico City, Abs. LBPEC21

- PHIA data from Eswatini, Lesotho, Malawi, Namibia, Tanzania, Uganda, Zambia, Zimbabwe

High ART Uptake in Women with Pregnancies Past 3 Years (N=2,332)

- Pooled ART Uptake: 93.6%
- Only 6.4% did not receive any ART
- Significant proportion on preconception ART (53%)

Diagnosis Infant HIV or Death, by Maternal ARV Status

- At 3 years:
  - HIV infection 9.1% (95% CI 8-11%)
  - Mortality: 6.5% (95% CI 5-8%)
- Most infant infections in infants born to mothers not receiving ART
PHIA 2015-2017: Survival and HIV-Free Survival in Children <3 Years

Saito S et al IAS July 2019, Mexico City Abs. LBPEC21

- PHIA data from Eswatini, Lesotho, Malawi, Namibia, Tanzania, Uganda, Zambia, Zimbabwe

**Child Survival to Age 3 Years by HIV Exposure**

- N=16,006
- Total children: 16,006
  - HIV-unexposed 13,633
  - HIV-exposed: 2,373 (14.8%)

**HIV-Free Survival in HIV-Exposed Infants by Maternal ART**

- N=2,370
- Overall: 85% at 3 years
  - HEU: 2,373
    - At 3 yr: 2152 uninfected
    - 118 infected
    - 103 died

Best HIV-free survival with preconception ART (fewest infant infections)
While progress has been made in PMTCT, it has significantly stalled in last few years – how do we reach the “last mile” to eMTCT?

Slowing decline in AIDS-related mortality in children – because global ART coverage only 54% and lower rate viral suppression than adults?

Adolescents as key target population:
- ↑ age of youth living with HIV globally, with poor viral suppression = increased risk of transmission to others?
- Young women remain at higher risk of HIV than young men.
- AIDS-related mortality has not declined among youth.

Importance of ensuring “survive and thrive” among increasing numbers of HIV-exposed but uninfected children?
Pre-Treatment ARV
Drug Resistance in Infants
Nationally Representative Surveys of Pretreatment HIVDR (PDR) among Infants < 18 Months Newly Diagnosed with HIV and ART-Naive (2012-2018)

Bertagnolio S. IAS July 2019, Mexico City

Countries with PDR surveys: 9 completed, 1 ongoing, 2 planned
Prevalence of NNRTI PDR in Infants, by Country

Bertagnolio S. IAS July 2019, Mexico City

1 out of 2 newly diagnosed infants have HIV with EFV/NVP resistance

NNRTI PDR ranges from 35% to nearly 70%!
Prevalence of NRTI PDR in Infants Newly Diagnosed with HIV, by Drug and Country

Bertagnolio S. IAS July 2019, Mexico City
Response in Countries with High PDR to NNRTI in Infants

Change to non-NNRTI 1st Line ART is Slow

NIGERIA: PDR to EFV/NVP 48.6%.
LPV-r is the preferred first-line ART for children <3 years in the national guidelines and discussions are ongoing to use DTG for children ≥20kg; however, NNRTIs are still the most commonly used first-line pediatric regimens (~91% of children).

TOGO: PDR to EFV/NVP 57.3%.
LPV-r is the preferred first-line ART in the national guidelines.

ZIMBABWE: PDR to EFV/NVP 63.9%.
LPV-r is the preferred first-line ART for children <3 years in the national guidelines and discussions are ongoing to use DTG for children ≥20kg; however, NNRTIs are still the most commonly used first-line pediatric regimens.

UGANDA: PDR to EFV/NVP 35.7%.
LPV-r is the preferred and most commonly used first-line ART for children <3 years. Discussions are ongoing to use DTG for children ≥20kg.

MALAWI: PDR to EFV/NVP 68.8%.
Adoption of LPV-r or INSTI as the preferred first-line ART in the national guidelines is in process; NNRTIs are currently the first-line pediatric regimens.

MOZAMBIQUE: PDR to EFV/NVP 56%.
LPV-r is the preferred first-line ART for children <3 years in the national guidelines and discussions are ongoing to use DTG for children ≥20kg; however, NNRTIs are still the most commonly used first-line pediatric regimens.

SOUTH AFRICA: PDR to EFV/NVP 63.7%.
LPV-r is the preferred and most commonly used first-line ART for children <3 years. Discussions are ongoing to use DTG for children ≥20kg.

ESWATINI: PDR to EFV/NVP 34.0%.
LPV-r is the preferred and most commonly used first-line ART for children <3 years. Discussions are ongoing to use DTG for children ≥20kg.
Case-control study to evaluate drug resistance in PROMISE.

At infant diagnosis, maternal drug resistance (DR) (primarily NNRTI) and VL independently associated with MTCT.

**Maternal VL at Time Infant Dx**

<table>
<thead>
<tr>
<th>Type of Mother-to-Child Transmission</th>
<th>Cases (MTCT)</th>
<th>Controls (No MTCT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>In utero/Peripartum</td>
<td>4.3</td>
<td>3.9</td>
</tr>
<tr>
<td>Breastfeeding</td>
<td>1</td>
<td>2.0</td>
</tr>
</tbody>
</table>

% Mothers with DR

- **Cases (MTCT)**
  - In utero/Peripartum: 14.6%
  - Breastfeeding: 6.2%

- **Controls (No MTCT)**
  - In utero/Peripartum: 6.2%
  - Breastfeeding: 4.3%

**Maternal DR Mutations**

- **Drug Class**: PI, NRTI, NNRTI
- **Mutations**:
  - PI: M41L, A83G, K103N
  - NRTI: V179D, Y181C, Y181C
  - NNRTI: K103N

**Multivariate Analysis**

OR (95% CI) p-value

- 24 Log c/mL Plasma Viral Load (<4 Log c/mL): 2.33 (1.29-4.21) 0.005
- DR Genotype (WT Genotype): 2.45 (1.03-5.81) 0.042

Adjusted for AP maternal ART, VL and genotype
At time HIV dx, prevalence of DR lower in infants with IU/peripartum vs BF MTCT (p<0.001).

- 25% of mother-infant pairs had discordant genotypes; 90% infants with DR had wild type (WT) mothers.

DR emerged over time in both groups of infants as they breastfed.

- Maternal NNRTI resistance may reduce efficacy of postnatal infant NVP prophylaxis?
- Would infant prophylaxis with drug with greater barrier to resistance be more effective?
- Primarily acquired as opposed to transmitted DR: exposure to infant NVP in early MTCT or maternal ART during BF leads to emergence DR in BF infants, even if mother WT.
Very high rates of pre-treatment drug resistance among newly infected infants - yet use of NNRTI-based 1st line ART remains common and may contribute to poor viral suppression on ART in children.

Pre-treatment drug resistance in infants:

- May be due to NNRTI-resistant virus transmission from mother to child (may reflect pre-treatment drug resistant virus transmitted to mother).
  - Possible that presence of maternal NNRTI-resistant virus reduces efficacy of infant NVP prophylaxis?
- May be due to early infant infection during exposure to NVP prophylaxis – or (potentially more likely) due to infant infection during exposure to subtherapeutic NNRTI drug levels in breast milk of mother on EFV ART.
Update: Dolutegravir and Pregnancy Outcome, Including Neural Tube Defects
Ability to Rule-Out An Increase in Birth Defects With Drug Exposure is Related to Defect Prevalence and Number of Observed Exposures

- 200 exposures can rule out a 2-fold ↑ in overall birth defects (prevalence 3%)

Ability to Rule-Out An Increase in Birth Defects With Drug Exposure is Related to Defect Prevalence and Number of Observed Exposures

- However, to rule-out a 3-fold increase in a rare event like NTD (prevalence 0.1%), need ~ 2,000 preconception exposures.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Teratogenic action</th>
<th>Risk of NTD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inadequate maternal nutritional status (e.g., folate)</td>
<td>Embryonic exposure to low folate levels or disturbed folate-related metabolism; RBC folate levels correlate with NTD risk</td>
<td>Crider K. BMJ 2014 If maternal RBC folate &lt;500 nmol/L, ~4x ↑ risk NTD compared to &gt;1000 nmol/L, where NTD risk 0.06%</td>
</tr>
<tr>
<td>Maternal diabetes</td>
<td>Embryonic exposure to high glucose leading to increased cell death in neuroepithelium</td>
<td>2 – 10-fold increase</td>
</tr>
<tr>
<td>Maternal obesity</td>
<td>Embryonic exposure to hyperinsulinemia, metabolic syndrome, oxidative stress</td>
<td>1.3 - 3.5-fold increase</td>
</tr>
<tr>
<td>Maternal hyperthermia</td>
<td>Embryonic exposure to heat stress</td>
<td>2-fold increase</td>
</tr>
<tr>
<td>Drugs (especially valproate)</td>
<td>Embryonic exposure to valproate; inhibitor of histone deacetylases, disturbing balance of protein acetylation and deacetylation leading to neurulation failure</td>
<td>10-fold increase</td>
</tr>
</tbody>
</table>
Tsepmo: NTD Prevalence, May 2018

- **DTG preconception**: May 2018, NTD 426, NTD 4
- **Non-DTG preconception**: May 2018, NTD 11300, NTD 14
- **EFV pre-conception**: May 2018, NTD 5787, NTD 3
- **HIV-uninfected**: May 2018, NTD 66057, NTD 61

→ Significant prevalence difference between DTG preconception and all other exposure groups (0.82 to 0.94)
Tsepamo: Evolution of NTD Prevalence Over Time - May 2018-March 2019

Zash R et al. IAS July 2019, Mexico City Abs. MOAX0105LB

Neural-Tube Defects and Antiretroviral Treatment Regimens in Botswana


Prevalence Difference
NTD by ARV/HIV Groups:
DTG Preconception vs Others

Difference 0.20 (0.01, 0.59)
Difference 0.26 (0.07, 0.66)
Difference 0.22 (0.05, 0.61)
While NTD prevalence has decreased with increased exposure numbers, it remains significantly different from other comparison categories.

Possible larger number of exposures needed to see resolution of signal (to detect 3-fold increase in risk of defect with prevalence 0.1%, need >2,000 exposures).

Or possible elevated risk will remain at this lower level.
Neural Tube Prevalence by Maternal ART Regimen and Timing

<table>
<thead>
<tr>
<th></th>
<th>Tsepamo data</th>
<th>Tsepamo data</th>
<th>Tsepamo data</th>
<th>Tsepamo data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of NTDs</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Number of Exposures</td>
<td>152</td>
<td>381</td>
<td>261</td>
<td>2328</td>
</tr>
<tr>
<td>% with NTD (95% CI)</td>
<td>0.66% (0.02%, 3.69%)</td>
<td>0 (0, 0.79%)</td>
<td>0 (0, 1.15%)</td>
<td>0.09% (0.01%, 0.31%)</td>
</tr>
<tr>
<td>Prevalence Difference (95% CI)</td>
<td>ref</td>
<td>0.66% (-0.73%, 4.16%)</td>
<td>0.66% (-1.25%, 4.16%)</td>
<td>0.58% (-0.10%, 4.10%)</td>
</tr>
</tbody>
</table>

MoH added 22 non-Tsepamo delivery sites in Botswana for birth surveillance; together with Tsepamo, cover 92% of all births in country.

Raesima M et al. IAS 2019 Abs. MOAX0106LB; NEJM 2019 Jul 22 Epub ahead of print
Case-control (1:3) study using registry linkage through national MoH databases to estimate NTD risk with periconception (±8 wk of estimated date conception) DTG vs non-DTG (EFV or RAL) ART.

- No NTD with periconception ART live births (defects in stillbirth/abortions not routinely reported).
- Note NTD prevalence in Brazil, with food folate fortification, is 0.06% (Santos LM. Bull WHO 2016); a 3-fold increase to 0.18% likely not be detectable with 384 exposures.

<table>
<thead>
<tr>
<th>Pregnancy outcome</th>
<th>Periconception Non-DTG (EFV or RAL) ART (N=1,068)</th>
<th>Periconception DTG ART (N=384)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live birth</td>
<td>1,025 (96%)</td>
<td>359 (93.5%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>15 (1.4%)</td>
<td>2 (0.5%)</td>
<td></td>
</tr>
<tr>
<td>Abortion (spontaneous miscarriage)</td>
<td>28 (2.6%)</td>
<td>23 (6.0%)</td>
<td></td>
</tr>
<tr>
<td>Birth defect</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any birth defect</td>
<td>62 (5.6%)</td>
<td>18 (4.7%)</td>
<td>0.50</td>
</tr>
<tr>
<td>NTD</td>
<td>0/1,068</td>
<td>0/384</td>
<td></td>
</tr>
<tr>
<td>Primary outcome: NTD, stillbirth or abortion</td>
<td>43 (4.0%)</td>
<td>25 (6.5%)</td>
<td>0.07</td>
</tr>
</tbody>
</table>
Periconception ARV Exposure and Neural Tube Defects: Antiretroviral Pregnancy Registry

Mofenson L et al. IAS July 2019, Mexico City Abs. TUAB0101

- 20,372 prospectively enrolled pregnancies through January 2019 with 20,727 birth outcomes; summarized overall, by drug class and for selected specific drugs.
  - Earliest timing of exposure was assigned to each drug:
    - **Periconception** – ARV exposure from 2 weeks before conception through ≤28 days after conception (6 weeks estimated gestational age [EGA])
    - **Later 1st trimester** – Initial exposure started later in the 1st trimester (after 6 weeks EGA)
    - **2nd/3rd trimester** – Exposure started after the 1st trimester ended (> 12 weeks EGA)
- Overall, 536 defects (2.8%): 51 CNS, including 8 NTD (0.04%) and 1 encephalocele.
- 8,546 with periconception exposure, 241 defects (2.8%): 23 CNS defects, including 3 NTD (0.04%), no encephaloceles.
<table>
<thead>
<tr>
<th>Periconception</th>
<th>ARV</th>
<th>Exposures</th>
<th>Any Defect</th>
<th>CNS Defects</th>
<th>Neural Tube Defect</th>
<th>Encephalocele</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any ART</td>
<td>8546</td>
<td>241</td>
<td>23</td>
<td>3 (0.03%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Periconception ARV</td>
<td>Exposures</td>
<td>Any Defect</td>
<td>CNS Defects</td>
<td>Neural Tube Defect</td>
<td>Encephalocele</td>
<td></td>
</tr>
<tr>
<td>-------------------</td>
<td>-----------</td>
<td>------------</td>
<td>-------------</td>
<td>-------------------</td>
<td>---------------</td>
<td></td>
</tr>
<tr>
<td>Any ART</td>
<td>8546</td>
<td>241</td>
<td>23</td>
<td>3 (0.03%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Any NRTI/NtRTI</td>
<td>8013</td>
<td>230</td>
<td>22</td>
<td>3 (0.04%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>ABC</td>
<td>1027</td>
<td>32</td>
<td>4</td>
<td>1 (0.10%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>FTC</td>
<td>2742</td>
<td>68</td>
<td>8</td>
<td>2 (0.07%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>3TC</td>
<td>4129</td>
<td>129</td>
<td>13</td>
<td>1 (0.02%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>TDF</td>
<td>3366</td>
<td>80</td>
<td>8</td>
<td>2 (0.06%)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>
## CNS & NTD by Drug Class with Periconception Exposure in APR

<table>
<thead>
<tr>
<th>Periconception ARV</th>
<th>Exposures</th>
<th>Any Defect</th>
<th>CNS Defects</th>
<th>Neural Tube Defect</th>
<th>Encephalocele</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any ART</strong></td>
<td>8546</td>
<td>241</td>
<td>23</td>
<td>3 (0.03%)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Any NRTI/NtRTI</strong></td>
<td>8013</td>
<td>230</td>
<td>22</td>
<td>3 (0.04%)</td>
<td>0</td>
</tr>
<tr>
<td>ABC</td>
<td>1027</td>
<td>32</td>
<td>4</td>
<td>1 (0.10%)</td>
<td>0</td>
</tr>
<tr>
<td>FTC</td>
<td>2742</td>
<td>68</td>
<td>8</td>
<td>2 (0.07%)</td>
<td>0</td>
</tr>
<tr>
<td>3TC</td>
<td>4129</td>
<td>129</td>
<td>13</td>
<td>1 (0.02%)</td>
<td>0</td>
</tr>
<tr>
<td>TDF</td>
<td>3366</td>
<td>80</td>
<td>8</td>
<td>2 (0.06%)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Any PI</strong></td>
<td>3830</td>
<td>112</td>
<td>9</td>
<td>1 (0.03%)</td>
<td>0</td>
</tr>
<tr>
<td>ATV</td>
<td>1067</td>
<td>25</td>
<td>3</td>
<td>1 (0.09%)</td>
<td>0</td>
</tr>
<tr>
<td>DRV</td>
<td>436</td>
<td>16</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>LPV/r</td>
<td>949</td>
<td>22</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Periconception ARV</td>
<td>Exposures</td>
<td>Any Defect</td>
<td>CNS Deects</td>
<td>Neural Tube Defect</td>
<td>Encephalocele</td>
</tr>
<tr>
<td>-------------------</td>
<td>-----------</td>
<td>------------</td>
<td>------------</td>
<td>-------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Any ART</td>
<td>8546</td>
<td>241</td>
<td>23</td>
<td>3 (0.03%)</td>
<td>0</td>
</tr>
<tr>
<td>Any NRTI/NtRTI</td>
<td>8013</td>
<td>230</td>
<td>22</td>
<td>3 (0.04%)</td>
<td>0</td>
</tr>
<tr>
<td>ABC</td>
<td>1027</td>
<td>32</td>
<td>4</td>
<td>1 (0.10%)</td>
<td>0</td>
</tr>
<tr>
<td>FTC</td>
<td>2742</td>
<td>68</td>
<td>8</td>
<td>2 (0.07%)</td>
<td>0</td>
</tr>
<tr>
<td>3TC</td>
<td>4129</td>
<td>129</td>
<td>13</td>
<td>1 (0.02%)</td>
<td>0</td>
</tr>
<tr>
<td>TDF</td>
<td>3366</td>
<td>80</td>
<td>8</td>
<td>2 (0.06%)</td>
<td>0</td>
</tr>
<tr>
<td>Any PI</td>
<td>3830</td>
<td>112</td>
<td>9</td>
<td>1 (0.03%)</td>
<td>0</td>
</tr>
<tr>
<td>ATV</td>
<td>1067</td>
<td>25</td>
<td>3</td>
<td>1 (0.09%)</td>
<td>0</td>
</tr>
<tr>
<td>DRV</td>
<td>436</td>
<td>16</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>LPV/r</td>
<td>949</td>
<td>22</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Any NNRTI</td>
<td>2304</td>
<td>57</td>
<td>5</td>
<td>1 (0.04%)</td>
<td>0</td>
</tr>
<tr>
<td>EFV</td>
<td>1037</td>
<td>25</td>
<td>3</td>
<td>1 (0.10%)</td>
<td>0</td>
</tr>
<tr>
<td>NVP</td>
<td>943</td>
<td>28</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>RPV</td>
<td>329</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Periconception ARV</td>
<td>Exposures</td>
<td>Any Defect</td>
<td>CNS Defects</td>
<td>Neural Tube Defect</td>
<td>Encephalocele</td>
</tr>
<tr>
<td>--------------------</td>
<td>-----------</td>
<td>------------</td>
<td>-------------</td>
<td>-------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Any ART</td>
<td>8546</td>
<td>241</td>
<td>23</td>
<td>3 (0.03%)</td>
<td>0</td>
</tr>
<tr>
<td>Any NRTI/NtRTI</td>
<td>8013</td>
<td>230</td>
<td>22</td>
<td>3 (0.04%)</td>
<td>0</td>
</tr>
<tr>
<td>ABC</td>
<td>1027</td>
<td>32</td>
<td>4</td>
<td>1 (0.10%)</td>
<td>0</td>
</tr>
<tr>
<td>FTC</td>
<td>2742</td>
<td>68</td>
<td>8</td>
<td>2 (0.07%)</td>
<td>0</td>
</tr>
<tr>
<td>3TC</td>
<td>4129</td>
<td>129</td>
<td>13</td>
<td>1 (0.02%)</td>
<td>0</td>
</tr>
<tr>
<td>TDF</td>
<td>3366</td>
<td>80</td>
<td>8</td>
<td>2 (0.06%)</td>
<td>x</td>
</tr>
<tr>
<td>Any PI</td>
<td>3830</td>
<td>112</td>
<td>9</td>
<td>1 (0.03%)</td>
<td>0</td>
</tr>
<tr>
<td>ATV</td>
<td>1067</td>
<td>25</td>
<td>3</td>
<td>1 (0.09%)</td>
<td>0</td>
</tr>
<tr>
<td>DRV</td>
<td>436</td>
<td>16</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>LPV/r</td>
<td>949</td>
<td>22</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Any NNRTI</td>
<td>2304</td>
<td>57</td>
<td>5</td>
<td>1 (0.04%)</td>
<td>0</td>
</tr>
<tr>
<td>EFV</td>
<td>1037</td>
<td>25</td>
<td>3</td>
<td>1 (0.10%)</td>
<td>0</td>
</tr>
<tr>
<td>NVP</td>
<td>943</td>
<td>28</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>RPV</td>
<td>329</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>InSTI</td>
<td>725</td>
<td>21</td>
<td>3</td>
<td>1 (0.14%)</td>
<td>0</td>
</tr>
<tr>
<td>DTG</td>
<td>248</td>
<td>9</td>
<td>2</td>
<td>1 (0.40%)</td>
<td>0</td>
</tr>
<tr>
<td>EVG</td>
<td>217</td>
<td>6</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>RAL</td>
<td>268</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Most APR reports come from North America, where there is national food folate fortification, which reduces NTDs risk by 36%-68% in the general population (Wang Nutr 2016; Williams MMWR 2015; Ray Food Nutr Bull 2008).

Overall NTD prevalence in 8,546 periconception ARV exposures was 0.03%; this frequency is consistent with the observed low NTD prevalence (0.01%-0.08%) in most developed countries with food fortification.

In the updated APR data, there is one NTD with 248 periconception DTG exposures, for prevalence 0.40% for DTG and 0.14% for InSTI, but this is based on only one NTD in relatively small number of exposures.

The number of pregnancies enrolled in the APR with InSTI periconception exposure are currently insufficient to rule out or confirm any potential association with NTD.
### Review of NTD with Preconception DTG: Published and New Data

<table>
<thead>
<tr>
<th>Study</th>
<th>Food Folate Fortification</th>
<th>#NTD/# PC Exposures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tsepamo 2019 confidential</td>
<td>No</td>
<td>5/1,683 (0.30%)</td>
</tr>
<tr>
<td>CDC-MOH Botswana 2019 confidential</td>
<td>No</td>
<td>1/152 (0.66%)</td>
</tr>
<tr>
<td>Sibiude, France (CROI 2019)</td>
<td>No</td>
<td>0/41</td>
</tr>
<tr>
<td>Chouchana, France (JAIDS 2019)</td>
<td>No</td>
<td>0/49</td>
</tr>
<tr>
<td>Thorne, EPPICC confidential</td>
<td>No</td>
<td>0/64</td>
</tr>
<tr>
<td>Weissmann, Germany (Glasgow 2018)</td>
<td>No</td>
<td>0/3</td>
</tr>
<tr>
<td>Kowalska, eastern Europe (Glasgow 2018)</td>
<td>No</td>
<td>0/24</td>
</tr>
<tr>
<td>Bornhede, Sweden (Eur J ID 2018)</td>
<td>No</td>
<td>0/14</td>
</tr>
<tr>
<td>Orrell, multicountry ARIA (Lancet HIV 2017)</td>
<td>No</td>
<td>0/1</td>
</tr>
<tr>
<td>APR Jan 2019 confidential</td>
<td>International registry (most)</td>
<td>1/248 (0.40%)</td>
</tr>
<tr>
<td>Brazil case-control confidential</td>
<td>Yes</td>
<td>0/384</td>
</tr>
<tr>
<td>PHACS, US confidential</td>
<td>Yes</td>
<td>0/157</td>
</tr>
<tr>
<td>Advance, S Africa (CROI 2018)</td>
<td>Yes</td>
<td>0/16</td>
</tr>
<tr>
<td>Money, Canada (BJOG 2019)</td>
<td>Yes</td>
<td>0/69</td>
</tr>
<tr>
<td>Grayhack, US (AIDS 2018)</td>
<td>Yes</td>
<td>0/28</td>
</tr>
</tbody>
</table>
### Review of NTD with Preconception DTG: Published and New Data

<table>
<thead>
<tr>
<th>Study</th>
<th>Food Folate Fortification</th>
<th>#NTD/# PC Exposures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tsepamo 2019 confidential</td>
<td>No</td>
<td>5/1,683 (0.30%)</td>
</tr>
<tr>
<td>CDC-MOH Botswana 2019 confidential</td>
<td>No</td>
<td>1/152 (0.66%)</td>
</tr>
<tr>
<td>Sibiude, France (CROI 2019)</td>
<td>No</td>
<td>0/41</td>
</tr>
<tr>
<td>Chouchana, France (JAIDS 2019)</td>
<td>No</td>
<td>0/49</td>
</tr>
<tr>
<td>Thorne, EPPICC confidential</td>
<td>No</td>
<td>0/64</td>
</tr>
<tr>
<td>Weissmann, Germany (Glasgow 2018)</td>
<td>No</td>
<td>0/3</td>
</tr>
<tr>
<td>Kowalska, eastern Europe (Glasgow 2018)</td>
<td>No</td>
<td>0/24</td>
</tr>
<tr>
<td>Bornhede, Sweden (Eur J ID 2018)</td>
<td>No</td>
<td>0/14</td>
</tr>
<tr>
<td>Orrell, multicountry ARIA (Lancet HIV 2017)</td>
<td>No</td>
<td>0/1</td>
</tr>
</tbody>
</table>

**No folate food fortification, DTG NTD prevalence**

6 NTD / 2,031 = **weighted estimate 0.36% (0.10-0.62)**

**No folate fortification, NTD pooled prevalence general population: 0.09-0.1%**

**DTG vs general population: ~3.6 to 4-fold increase**

<table>
<thead>
<tr>
<th>Study</th>
<th>Food Folate Fortification</th>
<th>#NTD/# PC Exposures</th>
</tr>
</thead>
<tbody>
<tr>
<td>APR Jan 2019 confidential</td>
<td></td>
<td>International registry (most) 1/248 (0.40%)</td>
</tr>
<tr>
<td>Brazil case - control confidential</td>
<td>Yes</td>
<td>0/384</td>
</tr>
<tr>
<td>PHACS, US confidential</td>
<td>Yes</td>
<td>0/157</td>
</tr>
<tr>
<td>Advance, S Africa (CROI 2018)</td>
<td></td>
<td>0/16</td>
</tr>
<tr>
<td>Money, Canada (BJOG 2019)</td>
<td>Yes</td>
<td>0/69</td>
</tr>
<tr>
<td>Grayhack, US (AIDS 2018)</td>
<td>Yes</td>
<td>0/28</td>
</tr>
</tbody>
</table>

**With folate food fortification, DTG NTD prevalence**

1 NTD / 901 = **weighted estimate 0.12% (0.0-0.34)**

**Folate fortification, NTD pooled prevalence general population: 0.06%**

**DTG vs general population: ~2-fold increase**
It is important to recognize

- Neural tube defect risk is not zero in the absence of drug
- The risk, of confirmed, is still relatively small: 1 in 1000 in the general population without folate food fortification, with potential 3-fold increase to 3 in 1000 – an excess of 2 NTD per 1,000 exposures
- Important to weigh risks against potential benefits

No drug exposure
No food folate fortification:
NTD prevalence 0.1%

If baseline population NTD prevalence lower, absolute number of NTD would be lower

Current Tsepamo preconception DTG NTD prevalence 0.30% = increase of 2 NTD per 1000 exposures
Countries with mandatory cereal grain fortification. Red countries have mandatory legislation for wheat flour, green countries for wheat and maize, orange for wheat and rice, blue for wheat, maize and rice, yellow for rice.


40-66% decrease in NTD in countries with folate food fortification

(Keats EF. Am J Clin Nutr. 2019
Kancherla V. Birth Defects Res. 2018
Crider KS. BJM. 2014
Das JK. Syst Rev. 2013)
Many of the countries with the heaviest burden of HIV – Africa, Eastern Europe, Asia – have no folate food fortification policies. 

In countries with folate food fortification (Keats EF. Am J Clin Nutr. 2019; Kancherla V. Birth Defects Res. 2018)

While protective effect of folate in women on DTG who wish to become pregnant not yet established, folate food fortification improves pregnancy outcomes in overall population.
Risk vs Benefits of DTG in Women of Childbearing-Potential at a Population Level

Myer L et al. IAS July 2019, Mexico City, Abs. WESY0105

CEPAC: May 2019 Tsepamo data, PDR 10.7%, DTG efficacy per recent trials

For every 1000 South African WCBP with HIV starting ART, per yr, compared with EFV (average over 5 yrs):

DTG only vs EFV only

→ DTG in all compared to EFV in all in 1,000 WCBP:
  • 1 excess NTD
  • More maternal survival, less transmission to sexual partners, less MTCT, resulting in higher HIV-free survival in infants

DTG with contraception vs EFV only

→ DTG with contraceptive vs EFV in 1,000 WCBP
  • Reducing unintended pregnancies in women using DTG effectively eliminates NTD concerns
  • Needs high coverage of effective methods
  • Reducing unintended pregnancies important goal of integrating contraceptive & family planning services into ART

Source: C Dugdale/WHO 2019
WHO Recommendations Update

2018

1. A dolutegravir (DTG)-based regimen is recommended as the preferred first-line regimen for people living with HIV initiating ART (conditional recommendation)
   - Adults and adolescents (moderate-certainty evidence)
   - Women and adolescent girls of childbearing potential (very low-certainty evidence)
   - Infants and children with approved DTG dosing (low-certainty evidence)

2. A raltegravir (RAL)-based regimen may be recommended as an alternative first-line regimen for infants and children for whom approved DTG dosing is not available (conditional recommendation, low-certainty evidence).

3. A RAL-based regimen is recommended as the preferred first-line regimen for neonates (conditional recommendation, very low-certainty evidence)

WHO 2016 consolidated guidelines on the use of ARV drugs for treating and preventing HIV infection.

2019

1. Dolutegravir (DTG) in combination with a nucleoside reverse-transcriptase inhibitor (NRTI) backbone is recommended as the preferred first-line regimen for people living with HIV initiating ART (strong recommendation, moderate-certainty evidence)
   - Adults and adolescents
   - Infants and children with approved DTG dosing (conditional recommendation, low-certainty evidence)

2. Efavirenz at low dose (EFV 400 mg) in combination with an NRTI backbone is recommended as the alternative first-line regimen for adults and adolescents living with HIV initiating ART (strong recommendation, moderate-certainty evidence)

3. A raltegravir (RAL)-based regimen may be recommended as the alternative first-line regimen for infants and children for whom approved DTG dosing is not available (conditional recommendation, low-certainty evidence)

4. A RAL-based regimen is recommended as the preferred first-line regimen for neonates (conditional recommendation, very low-certainty evidence)

*See Table 1 for ARV drug selection.

Exception in settings with pretreatment HIV drug resistance to EFV/nevirapine (NVP) exceeding 10%.
### Tsepamo: Major Structural Malformation (NTD, 14%): Differences by Exposure

Zash R et al. IAS July 2019, Mexico City Abs. MOAX0105LB; N Engl J Med 2019 Jul 22 epub

#### Exposure Group vs. Comparison Group

<table>
<thead>
<tr>
<th>Exposure Group vs. Comparison Group</th>
<th>Prevalence Difference (%) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTG at conception vs. Non-DTG at conception</td>
<td>0.27 (-0.13, 0.87)</td>
</tr>
<tr>
<td>DTG at conception vs. EFV at conception</td>
<td>0.26 (-0.16, 0.87)</td>
</tr>
<tr>
<td>DTG at conception vs. DTG start in pregnancy</td>
<td>0.51 (0.06, 1.12)</td>
</tr>
<tr>
<td>DTG at conception vs. Non-DTG start in pregnancy</td>
<td>0.31 (-0.12, 0.92)</td>
</tr>
<tr>
<td>DTG at conception vs. HIV-negative</td>
<td>0.36 (-0.01, 0.95)</td>
</tr>
</tbody>
</table>

#### No significant differences except comparing DTG started preconception vs during pregnancy

- **Overall Population**
  - N: 118,985
  - Defects: 719

- **DTG preconception**
  - N: 1,683
  - Defects: 16*

- **Non-DTG preconception**
  - N: 14,785
  - Defects: 101

- **EFV preconception**
  - N: 7,955
  - Defects: 55

- **DTG during pregnancy**
  - N: 3,836
  - Defects: 17

- **Non-DTG during pregnancy**
  - N: 5,948
  - Defects: 38

- **HIV-Uninfected**
  - N: 89,343
  - Defects: 528

*NTD (5); presumed holoprosencephaly (1); omphalocele (2); gastroschisis (2); club foot (2); upper limb defects (2), anophthalmia (1); skeletal dysplasia (1)
Pregnancy Outcomes: EFV vs DTG, Started During Pregnancy vs Before Conception

**Tsepamo Study**

**EFV or DTG Started During Pregnancy**

- **Any adverse outcome**
  - EFV/TDF/FTC (N=4,593): 35.0%
  - DTG/TDF/FTC (N=1,729): 33.2%

- **Any severe adverse outcome**
  - EFV/TDF/FTC (N=4,593): 11.3%
  - DTG/TDF/FTC (N=1,729): 10.7%

- **Preterm <37 wk GA**
  - EFV/TDF/FTC (N=4,593): 18.5%
  - DTG/TDF/FTC (N=1,729): 18.0%

- **Very preterm <32 wk GA**
  - EFV/TDF/FTC (N=4,593): 3.5%
  - DTG/TDF/FTC (N=1,729): 3.8%

- **SGA 10%ile wt for GA**
  - EFV/TDF/FTC (N=4,593): 18.5%
  - DTG/TDF/FTC (N=1,729): 17.4%

- **Very SGA 3%ile wt for GA**
  - EFV/TDF/FTC (N=4,593): 6.7%
  - DTG/TDF/FTC (N=1,729): 6.1%

- **Stillbirth**
  - EFV/TDF/FTC (N=4,593): 2.3%
  - DTG/TDF/FTC (N=1,729): 2.3%

- **Neonatal death**
  - EFV/TDF/FTC (N=4,593): 1.3%
  - DTG/TDF/FTC (N=1,729): 1.0%

**EFV or DTG Started Before Conception**

- **Any adverse outcome**
  - EFV/TDF/FTC (N=7,557): 35.0%
  - DTG/TDF/FTC (N=1,508): 33.2%

- **Any severe adverse outcome**
  - EFV/TDF/FTC (N=4,593): 12.8%
  - DTG/TDF/FTC (N=1,729): 11.9%

- **Preterm <37 wk GA**
  - EFV/TDF/FTC (N=4,593): 19.2%
  - DTG/TDF/FTC (N=1,729): 18.9%

- **Very preterm <32 wk GA**
  - EFV/TDF/FTC (N=4,593): 4.9%
  - DTG/TDF/FTC (N=1,729): 4.6%

- **SGA 10%ile wt for GA**
  - EFV/TDF/FTC (N=4,593): 18.2%
  - DTG/TDF/FTC (N=1,729): 17.0%

- **Very SGA 3%ile wt for GA**
  - EFV/TDF/FTC (N=4,593): 7.3%
  - DTG/TDF/FTC (N=1,729): 6.5%

- **Stillbirth**
  - EFV/TDF/FTC (N=7,557): 2.0%
  - DTG/TDF/FTC (N=1,508): 2.6%

- **Neonatal death**
  - EFV/TDF/FTC (N=7,557): 1.6%
  - DTG/TDF/FTC (N=1,508): 1.0%

Zash R et al. Lancet Global Health 2018;6:e804-10

Zash R et al. IAS July 2019, Mexico City Abs. MOAX0105LB; N Engl J Med 2019 Jul 22 epub
Pregnancy Outcomes Among HIV-Positive Women Who Became Pregnant in ADVANCE Trial of DTG vs EFV ART Week 48 Analysis

Chandiwana N et al. IAS July 2019, Mexico City Abs. WEPEB280

- ADVANCE trial compared DTG/TDF/FTC vs DTG/TAF/FTC vs EFV/TDF/FTC; enrolled 1,053 ART-naïve women; 623 on DTG arms, 201 EFV arm
- Annual pregnancy rate 13%: 83 pregnancies, all ART before conception, had 1st trimester dating & 2nd trimester anomaly ultrasound; women on DTG switched if ≤ 8 wks gestation.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Overall</th>
<th>DTG overall (N=422)</th>
<th>DTG/TAF/FTC (N=214)</th>
<th>DTG/TDF/FTC (N=208)</th>
<th>EFV/TDF/FTC (N=201)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total pregnancies</strong></td>
<td>83</td>
<td>54 (13%)</td>
<td>29 (14%)</td>
<td>25 (12%)</td>
<td>29 (14%)</td>
</tr>
<tr>
<td><strong>Ongoing pregnancies</strong></td>
<td>9</td>
<td>8 (15%)</td>
<td>3 (10%)</td>
<td>5 (20%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td><strong>LTFU</strong></td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Pregnancy outcomes</strong></td>
<td>73 (88%)</td>
<td>46 (85%)</td>
<td>26 (90%)</td>
<td>20 (80%)</td>
<td>27 (93%)</td>
</tr>
<tr>
<td>Miscarriage &lt;20 wk GA</td>
<td>16 (22%)</td>
<td>7 (15%)</td>
<td>7 (27%)</td>
<td>0</td>
<td>9 (33%)</td>
</tr>
<tr>
<td>Stillbirth &gt;28 wk GA</td>
<td>1 (1.4%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Elective abortion</td>
<td>18 (25%)</td>
<td>14 (30%)</td>
<td>7 (27%)</td>
<td>7 (35%)</td>
<td>4 (15%)</td>
</tr>
<tr>
<td><strong>Live birth</strong></td>
<td>37 (51%)</td>
<td>24</td>
<td>11</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>SGA</td>
<td>7 (19%)</td>
<td>3 (12.5%)</td>
<td>1 (9%)</td>
<td>2 (15%)</td>
<td>4 (31%)</td>
</tr>
<tr>
<td>Neonatal death</td>
<td>1 (2.7%)</td>
<td>1 (4.2%)</td>
<td>1 (9%)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

- 3 minor birth defects (polydactyly; umbilical hernia; naevus flammeus); no NTD
Pregnancy Outcomes Among HIV-Positive Women Who Became Pregnant in ADVANCE Trial of DTG vs EFV ART Week 48 Analysis

Chandiwana N et al. IAS July 2019, Mexico City: Abs. WEPEB280

- ADVANCE Trial compared DTG/TDF/FTC vs DTG/TAF/FTC vs EFV/TDF/FTC; enrolled 1,053 ART-naïve women; 623 on DTG arms, 201 EFV arm
- Annual pregnancy rate 13%: 83 pregnancies, all ART before conception, had 1st trimester dating & 2nd trimester anomaly ultrasound; women on DTG switched if ≤ 8 wks gestation.

Outcomes

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Total pregnancies</th>
<th>Ongoing pregnancies</th>
<th>LTFU</th>
<th>Pregnancy outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Miscarriage &lt;20 wk GA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>73 (88%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>46 (85%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>26 (90%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>25 (12%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>29 (14%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>29 (14%)</td>
</tr>
</tbody>
</table>

- Small number preconception exposures.
- No NTD in 37 live births with preconception DTG exposure.
- Higher rates of elective abortions with preconception DTG vs EFV exposure – concern following NTD signal in Tsepamo?
- No excess stillbirth/miscarriage or adverse outcomes with preconception DTG vs EFV.

- 3 minor birth defects (polydactyly; umbilical hernia; naevus flammeus); no NTD
Weight Gain During Pregnancy in Women with HIV Starting DTG vs EFV vs Uninfected Women in Botswana, Tsepamo

Caniglia E et al. IAS July 2019, Mexico City Abs. LBPEB14

- Evaluated rate of weekly weight gain and weight gain between 18±2 to 36±2 wk GA
- Exposure groups for weight gain analysis
  - HIV+ women starting DTG btn conception and 17 wk GA (1st ANC wt 65.6 kg)
  - HIV+ women starting EFV btn conception and 17 wk GA (1st ANC wt 65.7 kg)
  - HIV-uninfected women of similar age, presenting for ANC <17 wk (1st ANC wt 66.5 kg)

![Adjusted Mean Difference Weekly Weight Gain (kg/wk)](chart1)

![Adjusted Mean Difference Weight Gain 18-36 wk (kg)](chart2)

Adjusted for: age, CD4, employment, education, parity, gravidity, marital status, site, smoking, alcohol, pre-pregnancy weight, weight at ART initiation (or first ANC), gestational age at ART initiation (or first ANC)
Weight Gain During Pregnancy in Women with HIV
Starting DTG vs EFV vs Uninfected Women in Botswana, Tsepamo

Caniglia E et al. IAS July 2019, Mexico City Abs. LBPEB14

- Evaluated rate of weekly weight gain and weight gain between 18±2 to 36±2 wk GA
- Exposure groups for weight gain analysis
  - HIV+ women starting DTG btn conception and 17 wk GA (1st ANC wt 65.6 kg)
  - HIV+ women starting EFV btn conception and 17 wk GA (1st ANC wt 65.7 kg)
  - HIV-uninfected women of similar age, presenting for ANC <17 wk (1st ANC wt 66.5 kg)

Adjusted Mean Difference Weight Gain 18-36 wk (kg)
Adjusted Mean Difference Weekly Weight Gain (kg/wk)

→ Women initiating DTG compared to EFV gained more weight btn 18-36 wk GA, especially in those with higher pre-ART pregnancy weight.

→ However, neither group gained as much weight as HIV-uninfected women.
Summary

▪ Preconception DTG NTD signal, while significantly diminished, remains significantly different than all other exposure groups; validated by Botswana MOH and APR data.

▪ Possible with additional exposures signal may resolve, but possible will remain at ~3-fold ↑, similar to maternal diabetes and obesity.

▪ Two analyses have shown benefits of DTG in women of childbearing potential outweigh potential risks; integration of SRH into HIV care would further decrease risk.

▪ Other adverse pregnancy outcomes do not appear to be different between preconception DTG and EFV.

▪ WHO now recommends DTG as preferred 1\textsuperscript{st}/2\textsuperscript{nd} line for all adults and children with dosing information as strong recommendation.

▪ While ↑ weight gain with DTG in pregnancy, still less than HIV- women.
Pregnancy, Contraception, ARVs, Viral Load, and Pregnancy Outcome
Low Pregnancy Incidence in Women on Different Contraceptives ECHO Trial

Onono M. IAS July 2019, Mexico City Abs. MOAX0103LB

- ECHO trial randomized HIV-negative women to DMPA (N=2,593), levonorgestrol implant (N=2,592) or copper IUD (N=2,525).

- Compared pregnancy incidence.

255 pregnancies reported

185 after stopped contraceptive method

85 with typical use

70 with perfect use

Median days from randomization to 1st pregnancy with perfect use:
- DMPA-IM, 96 days
- LNG implant, 108 days
- Copper IUD, 252 days

→ All contraceptives were highly effective (pregnancy incidence S Africa 25.1/100 WY, Chetty—Makkan, PLoSOne 2014).

→ Potential IUD partial/complete asymptomatic expulsion between visits may account for slightly higher pregnancy rate with IUD.

Perfect Use

Pregnancy Incidence per 100 WY; Pregnancies (n)

<table>
<thead>
<tr>
<th>Method</th>
<th>Incidence (95%CI)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMPA-IM</td>
<td>1.06 (0.72-1.50)</td>
<td>31</td>
</tr>
<tr>
<td>Copper IUD</td>
<td>0.63 (0.39-0.96)</td>
<td>21</td>
</tr>
<tr>
<td>LNG implant</td>
<td>0.61 (0.36-0.96)</td>
<td>18</td>
</tr>
</tbody>
</table>

No significant differences

Typical Use

Pregnancy Incidence per 100 WY; Pregnancies (n)

<table>
<thead>
<tr>
<th>Method</th>
<th>Incidence (95%CI)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMPA-IM</td>
<td>1.11 (0.77-1.54)</td>
<td>35</td>
</tr>
<tr>
<td>Copper IUD</td>
<td>0.87 (0.58-1.25)</td>
<td>29</td>
</tr>
<tr>
<td>LNG implant</td>
<td>0.63 (0.39-0.96)</td>
<td>21</td>
</tr>
</tbody>
</table>

P=0.044 IUD vs LNG
Evaluated maternal virologic suppression and infant HIV outcomes among WLWH on EFV ART with documented maternal VL at/near delivery and infant HIV status in 12 high volume antenatal clinics within urban Lusaka.

287 mother-infant pairs were analyzed with 271 (94%) women started or transitioned to EFV400 during pregnancy, 16 (6%) remained on EFV600.

69% started ART in pregnancy (median duration 4.8 mo), 41% receiving ART at conception

Maternal viral suppression at delivery was 92% (95% CI: 89,96%) among those receiving EFV400 and 88% among those receiving EFV600.

HIV DNA PCR was positive in 2 (0.7%) of the HIV exposed infants, with 3 (1.04%) non-viable outcomes and 0 fetal abnormalities.
In Utero Infection Does Not Differ in Women on DTG vs EFV ART, Botswana

Davey S et al  IAS July 2019, Mexico City  Abs. LBPEC30

- Early Infant Treatment Study tested HEU at <96 hours; of 10,622 tested, 40 (0.4%) HIV+
- Linked 5,064 to Tsepamo database for information maternal ART.
- No difference IU MTCT between those exposed to DTG (0.65%) vs EFV (0.37%) overall.
- While highest MTCT with late (<30d) ART start, no difference DTG vs EFV.

<table>
<thead>
<tr>
<th>Type of ART Initiation</th>
<th>Total (N=1,882)</th>
<th>DTG/TDF/FTC (N=998)</th>
<th>EFV/TDF/FTC (N=883)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ART initiated during pregnancy (n = 1,882)</td>
<td>16 / 1,882 (0.85%)</td>
<td>8 / 999 (0.80%)</td>
<td>8 / 883 (0.91%)</td>
</tr>
<tr>
<td>ART initiated &gt;180 days before delivery (n = 370)</td>
<td>2 / 370 (0.54%)</td>
<td>1 / 223 (0.45%)</td>
<td>1 / 136 (0.74%)</td>
</tr>
<tr>
<td>ART initiated 90-179 days before delivery (n = 1,128)</td>
<td>4 / 1,128 (0.35%)</td>
<td>3 / 568 (0.53%)</td>
<td>1 / 537 (0.19%)</td>
</tr>
<tr>
<td>ART initiated 30-89 days before delivery (n= 351)</td>
<td>5 / 351 (1.42%)</td>
<td>1 / 170 (0.59%)</td>
<td>4 / 168 (2.38%)</td>
</tr>
<tr>
<td>ART initiated &lt;30 days before delivery (n = 82)</td>
<td>5 / 82 (6.10%)</td>
<td>3 / 38 (7.89%)</td>
<td>2 / 42 (4.76%)</td>
</tr>
<tr>
<td>ART initiation date missing (n = 55)</td>
<td>0 / 55 (0.0%)</td>
<td>0 / 23 (0.0%)</td>
<td>0 / 31 (0.0%)</td>
</tr>
</tbody>
</table>

Risk highest with start ART <30 d prior to delivery

[In utero MTCT for DTG or EFV started in pregnancy, for EIT and Tsepamo linked infants in Botswana]
Purpose to describe maternal viral load at delivery and IU MTCT rates in 4 tertiary care ob units in Johannesburg, June 2018-Mar 2019 with POC EID and VL testing (testing weekdays 8-4).

<table>
<thead>
<tr>
<th>Live births to HIV-positive woman</th>
<th>Valid VL result</th>
<th>Maternal PoC VL</th>
<th>Neonatal PoC EID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>8 147</td>
<td>2 769 (34.0%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 007 (36.4%)</td>
<td>4 333 (53.2%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>690 (24.9%)</td>
<td>621 (22.4%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>621 (22.4%)</td>
<td></td>
</tr>
</tbody>
</table>

### Methodology: Procedures

- **PCR Positive**: Confirmatory tests done on same sample + 2nd sample referred for care
- **PCR Negative**: Reassured and counselled to return for testing at 10 weeks
- **VL ≥1 000 copies/ml**: Adherence counselling for mother, high-risk prophylaxis for infant
- **VL <1 000 copies/ml**: Mother reassured about VL suppression, low-risk prophylaxis for infant

### Live births to HIV-positive woman and results
- **Valid VL**: 2 769 (34.0%)
- **VL ≥50 cps/ml**: 1 007 (36.4%)
- **VL ≥400 cps/ml**: 690 (24.9%)
- **VL ≥1 000*: 621 (22.4%)

### Neonatal PoC EID
- **Valid EID result**: 4 333 (53.2%)
- **PCR positive N (%)**: 65 (1.5%)

---

N, number; VL, viral load; EID, early infant diagnosis; cps/ml, copies per millilitre; PCR, polymerase chain reaction; PoC, Point-of-care

*Of those with VL ≥50, 32% were 50-399; 10% were 400-999; in the 62% with VL >1,000, median VL= 24 600 copies/mL (IQR: 6 380–82 100)
Impact of HIV and Obesity on Pregnancy Outcomes in Women In South Africa: Dual Epidemics

*Bengtson A et al. IAS July 2019, Mexico City Abs. TUAB0105*

- Birth outcome by HIV status: more C/S and LGA in HIV-uninfected, more PTD, LBW and SGA in HIV+ women on ART

<table>
<thead>
<tr>
<th>Pregnancy Outcome</th>
<th>HIV-uninfected</th>
<th>HIV-infected</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=413</td>
<td>N=464</td>
<td>N=877</td>
</tr>
<tr>
<td>Cesarean delivery</td>
<td>156 (37.8)</td>
<td>141 (30.4)</td>
<td>297 (33.9)</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>39 (9.4)</td>
<td>54 (11.6)</td>
<td>93 (10.6)</td>
</tr>
<tr>
<td>LBW</td>
<td>37 (9.0)</td>
<td>58 (12.5)</td>
<td>95 (10.8)</td>
</tr>
<tr>
<td>Small for gestational age (SGA)</td>
<td>45 (10.9)</td>
<td>55 (11.8)</td>
<td>100 (11.4)</td>
</tr>
<tr>
<td>Large for gestational age (LGA)</td>
<td>67 (16.2)</td>
<td>28 (6.0)</td>
<td>95 (10.8)</td>
</tr>
<tr>
<td>Birthweight, g (median, IQR)</td>
<td>3220 (2850, 3500)</td>
<td>3150 (2765, 3400)</td>
<td>3180 (2820, 3460)</td>
</tr>
</tbody>
</table>

*unless otherwise noted.*
Impact of HIV and Obesity on Pregnancy Outcomes in Women in South Africa: Dual Epidemics

Bengtson A et al. IAS July 2019, Mexico City Abs. TUAB0105

<table>
<thead>
<tr>
<th>BMI Category</th>
<th>Overall (N=877)</th>
<th>CESAREAN (N=264)</th>
<th>PRETERM (N=80)</th>
<th>LBW (N=82)</th>
<th>SGA (N=90)</th>
<th>LGA (N=90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obese</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BMI Category</th>
<th>HIV-infected (n=464)</th>
<th>HIV-uninfected (n=413)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obese</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HIV+ associated with adverse outcomes vs HIV- with normal BMI
Adverse Pregnancy Outcomes Among Women with HIV on ART Compared to HIV-Uninfected Women

Tukey VJ et al. IAS July 2019, Mexico City Abs. TUAB0102

- IMPROVE prospective cohort facility-based intervention to improve PMTCT services in Lesotho; enrolled 614 HIV+, 390 HIV- pregnant women.
- All HIV+ women received ART (89% EFV/TDF/FTC).
- Delivery outcome available for 564 (91.9%) HIV+ & 342 (88%) HIV- women.

<table>
<thead>
<tr>
<th>Adverse pregnancy outcome</th>
<th>HIV-Negative (N=342)</th>
<th>HIV-Positive (N=564)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite: Any adverse outcome (intrauterine loss, preterm, low birth weight, birth defect)</td>
<td>37/342 (10.8%)</td>
<td>117/564 (20.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intrauterine death overall</td>
<td>8/342 (2.3%)</td>
<td>44/564 (7.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Miscarriage (&lt;28 weeks)</td>
<td>2/342 (0.6%)</td>
<td>21/564 (3.7%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Stillbirth (≥28 weeks)</td>
<td>6/338 (1.8%)</td>
<td>23/543 (4.2%)</td>
<td>0.052</td>
</tr>
<tr>
<td>Any birth defect</td>
<td>4/337 (1.2%)</td>
<td>6/538 (1.1%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Premature (&lt;37 weeks)*</td>
<td>10/330 (3.0%)</td>
<td>25/517 (4.8%)</td>
<td>0.220</td>
</tr>
<tr>
<td>Low birth weight (&lt;2500 g)</td>
<td>22/304 (7.2%)</td>
<td>61/477 (12.8%)</td>
<td>0.017</td>
</tr>
<tr>
<td>Term low birth weight (≥37 weeks &amp; &lt;2500 g)</td>
<td>13/293 (4.45)</td>
<td>44/453 (9.7%)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

*prematurity live-born infants, excludes stillbirth
## Multivariate analysis: Adjusted Odds Adverse Outcome HIV+ vs HIV- Women

<table>
<thead>
<tr>
<th>Adverse Pregnancy Outcome</th>
<th>Overall Population</th>
<th>Subset with syphilis testing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Adjusted Odds Ratio * (95% CI)</td>
</tr>
<tr>
<td>Composite: Any adverse pregnancy outcome</td>
<td>873</td>
<td>2.29 (1.41-3.72)</td>
</tr>
<tr>
<td>Intrauterine loss (miscarriage or stillbirth)</td>
<td>873</td>
<td>2.86 (1.25-6.53)</td>
</tr>
<tr>
<td>Prematurity*</td>
<td>816</td>
<td>1.41 (0.57-3.49)</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>755</td>
<td>2.29 (1.34-3.90)</td>
</tr>
<tr>
<td>Term low birth weight</td>
<td>721</td>
<td>2.99 (1.49-6.03)</td>
</tr>
</tbody>
</table>

*Model adjusted for maternal age, estimated gestational age at enrollment, gravidity, and education

^Model adjusted for maternal age, estimated gestational age at enrollment, gravidity, education, and syphilis
# Adverse Pregnancy Outcomes Among Women with HIV

No Difference by Timing ART (Preconception vs During Pregnancy)

**Tukei VJ et al. IAS July 2019, Mexico City Abs. TUAB0102**

<table>
<thead>
<tr>
<th>Adverse pregnancy outcome</th>
<th>Pre-conception (N=282)</th>
<th>During pregnancy (N=268)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miscarriage (&lt;28 weeks)</td>
<td>14/282 (5.0%)</td>
<td>7/268 (2.6%)</td>
<td>0.184</td>
</tr>
<tr>
<td>Stillbirth (≥28 weeks)</td>
<td>11/268 (4.1%)</td>
<td>11/261 (4.2%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Prematurity (&lt;37 weeks)*</td>
<td>12/256 (4.7%)</td>
<td>13/248 (5.2%)</td>
<td>0.839</td>
</tr>
<tr>
<td>Low birth weight (&lt;2500 g)*</td>
<td>34/232 (14.7%)</td>
<td>25/233 (10.7%)</td>
<td>0.213</td>
</tr>
<tr>
<td>Any birth defect†</td>
<td>2/267 (0.8%)</td>
<td>4/258 (1.6%)</td>
<td>0.443</td>
</tr>
</tbody>
</table>

* Excludes stillbirths
† Includes stillbirths

*Women without data on timing of initiation (N=34) excluded from this analysis; live-born infants only, excludes stillbirth
Adverse Pregnancy Outcome, HIV-Infected vs Uninfected Women by Type of Delivery Health Center, Blantyre, Malawi

Kanyenda RC et al. IAS July 2019, Mexico City Abs WEPEB202

- Jan 2016-Aug 2017 registry from one large tertiary hospital and 4 primary care facilities
- 14,667 women with singleton live-birth or stillbirth >20 wk gestation
- 87% HIV-uninfected, 12% HIV+, 1% HIV unknown; HIV+ women older and higher gravida and 80% preconception ART

<table>
<thead>
<tr>
<th></th>
<th>HIV-uninfected N=12,714</th>
<th>HIV-Infected N=1,688</th>
<th>Adjusted Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low birth weight</td>
<td>1,275 (10%)</td>
<td>220 (13%)</td>
<td>1.51 (1.28-1.70)</td>
</tr>
<tr>
<td>Preterm</td>
<td>4,258 (34%)</td>
<td>586 (35%)</td>
<td>1.21 (1.07-1.36)</td>
</tr>
</tbody>
</table>

- Association of adverse birth outcome with HIV-infection/ART differed by delivery setting (low risk/primary health center vs high risk/tertiary health center).

<table>
<thead>
<tr>
<th></th>
<th>HIV-uninfected</th>
<th>HIV-infected</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary HC (N=6,605)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low birth weight</td>
<td>377 (6%)</td>
<td>49 (7%)</td>
<td>0.70</td>
</tr>
<tr>
<td>Preterm</td>
<td>2507 (43%)</td>
<td>307 (43%)</td>
<td>0.96</td>
</tr>
<tr>
<td><strong>Tertiary HC (N=7,797)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low birth weight</td>
<td>898 (13%)</td>
<td>171 (18%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Preterm</td>
<td>1751 (26%)</td>
<td>279 (29%)</td>
<td>0.03</td>
</tr>
</tbody>
</table>
Prospective cohort 1,087 uninfected, 205 HIV+ preconception ART, 99 HIV+ post-conception ART; PTD higher in HIV+ women

Evaluated pro- and anti-inflammatory cytokines plasma and vagina

Cross-sectional analysis: at 16-20 wk GA, HIV+ women before start ART have higher inflammation in GU than uninfected women but similar to those on ART

Pro-inflammatory score in vaginal fluid correlates with PTD
Zambian Preterm Birth Prevention Study (ZAPPS): Vaginal Inflammation is Associated with Starting ART in Pregnancy and Preterm Birth

De Paris K et al. IAS July 2019, Mexico City Abs. TUAB0103

- Longitudinal evaluation: At 24-34 wk GA, increased GU inflammation in HIV+ women starting ART compared same woman before ART (no difference plasma)

- Differences in inflammatory milieu linked to distinct vaginal microbiome composition (↑ G.vaginalis)
Summary

- Contraception of various modalities (DMPA, LNG implant, IUD) highly effective and safe in women in Africa.
- While ART effective in pregnancy, ~20% women lack suppression at delivery, although in utero MTCT rates remain low.
- Obesity is associated with adverse pregnancy outcomes in the overall population – but increase in adverse outcomes in women with HIV of normal BMI compared to women without HIV.
- Initiation of ART associated with inflammatory changes in the vaginal tract and change in microbiome.
- Such changes may be associated with increase in PTD.
- Despite ART, women with HIV appear to have increased adverse pregnancy outcomes compared to women without HIV.
PMTCT Cascade
In 2018, Zimbabwe began routine case-reporting for all new HIV infections in children 0-24 mos - FACE HIV Program supported MOH with analysis of case reports from facilities in 6 provinces, Jan-Sept 2018.

**ANC Service Uptake Mothers of HIV+ Infants (N=106)**

<table>
<thead>
<tr>
<th>ANC Uptake</th>
<th>MCH/PMTCT Service Uptake N (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No ANC Booking</td>
<td>40 (37.5)</td>
<td>11 (10.4)</td>
</tr>
<tr>
<td>Not documented</td>
<td>7 (5.8)</td>
<td>4 (3.9)</td>
</tr>
<tr>
<td>ANC Booking</td>
<td>53 (49.5)</td>
<td>55 (51.7)</td>
</tr>
<tr>
<td>Total</td>
<td>94 (88.9)</td>
<td>63 (58.5)</td>
</tr>
</tbody>
</table>

→ 10% (11/106) mothers of HIV+ infants not booked for ANC (national coverage 97%)
→ Significant association no/undocumented ANC with home delivery, no infant prophylaxis and no infant ART if infant HIV+

**Time on ART for Mothers of HIV+ Infants (N-106)**

→ Only 23% mothers had known HIV status before current pregnancy
→ 26% first tested HIV+ in L/D or postnatal care
→ 28% not tested or not documented test

→ Role of late diagnosis, limited time on ART, lack VL testing as primary risk factors
Enrolled 128 HIV+ women previously on ART but off ART for >3 weeks attending 1st ANC visit in Lilongwe Malawi 2015-2019.

- Primary reason for defaulting was treatment access, primarily due to relocation.
- Significantly longer time to reinitiate ART in women who did not disclose to partner, had ART side effects, or reported a religious reason for stopping ART.
Tshilo Dikotla Study, Botswana: Monitoring/Support of BF Women

Mulenga L et al. IAS July 2019, Mexico City Abs. LBPEB15

- Tshilo Dikotla study enrolls pregnant women 16-36 wk GA on EFV or DTG ART with intention to BF; infant randomized to AZT or NVP prophylaxis x4 wk. Analysis singleton infants with PCR 6 wk after cessation BF.

- Monitoring:
  - Maternal VL is obtained at enrollment, if >40 c/mL, repeated in pregnancy and at delivery.
  - During BF, VL monitoring and ART adherence education occur at each study visit (1, 2, 4-6, 9-12, 18, 24 months postpartum). If VL >40 c/mL, encouraged to change to FF.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N=129</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>30 yr (26-35)</td>
</tr>
<tr>
<td>Gravidity</td>
<td>3 (2-4)</td>
</tr>
<tr>
<td>CD4 &lt;200</td>
<td>14 (11%)</td>
</tr>
<tr>
<td>Duration BF</td>
<td>4 mo (1.7-6.0)</td>
</tr>
<tr>
<td>Maternal ART: DTG / EFV</td>
<td>86 (67%) / 43 (33%)</td>
</tr>
<tr>
<td>Infant prophylaxis arm: AZT / NVP</td>
<td>62 (48%) / 67 (52%)</td>
</tr>
<tr>
<td>VL &gt;40 during BF</td>
<td>13 (10%)</td>
</tr>
<tr>
<td>Switch to FF after VL &gt;40</td>
<td>8/13 (62%)</td>
</tr>
<tr>
<td>BF transmission</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

→ No postnatal infections
→ Intensive maternal VL during BF
→ 62% women with detectable VL during BF switched to FF feeding
Summary

▪ “Missed opportunity” analysis of cases of perinatal transmission and reasons for defaulting from care are useful in determining where gaps are in the PMTCT cascade.

▪ Breastfeeding transmission can be minimized with efforts targeted to VL monitoring and adherence counseling in the postpartum lactation period.
ARV Drugs in Children
PK of DTG 5 mg Dispersible Tablets in Children 6–<20 Kg

Waalewijn H et al. IAS July 2019, Mexico City Abs. WEAB0401LB

- ODYSSEY is a randomised, non-inferiority trial evaluating efficacy and safety of 1\textsuperscript{st} and 2\textsuperscript{nd} line DTG ART vs standard of care in 700 HIV-infected children <18 years (recruiting add 80 children <14 kg)

<table>
<thead>
<tr>
<th>WHO Weight bands, kg</th>
<th>DTG DT* once daily (# tablets, daily dose, mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 to &lt;6 (&lt;6 months old)</td>
<td>3 (15mg)</td>
</tr>
<tr>
<td>3 to &lt;6 (&gt;6 months old)</td>
<td>2 (10mg)</td>
</tr>
<tr>
<td>6 to &lt;10</td>
<td>3 (15mg)</td>
</tr>
<tr>
<td>10 to &lt;14</td>
<td>4 (20mg)</td>
</tr>
<tr>
<td>14 to &lt;20</td>
<td>5 (25mg)</td>
</tr>
<tr>
<td>20 to &lt;25</td>
<td>6 (30mg)</td>
</tr>
</tbody>
</table>

*DTG dispersible tablet (DT) formulation; DT are ~1.6 to 2.0x more bioavailable than film coated tablets (FCT)

4/11 (36%) had $C_{\text{trough}}$ values below $EC_{90}$ (0.32 mg/L)

<table>
<thead>
<tr>
<th>WHO weight band</th>
<th>ODYSSEY Weight Bands</th>
<th>Reference adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose mg/formulation</td>
<td>6–&lt;10</td>
<td>10–&lt;14</td>
</tr>
<tr>
<td>N</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Dose/weight (range) mg/kg</td>
<td>1.8 (1.5–2.2)</td>
<td>1.8 (1.6–2.0)</td>
</tr>
<tr>
<td>$C_{\text{trough}}$ (CV%) mg/L</td>
<td>0.48 (167)</td>
<td>0.82 (55)</td>
</tr>
<tr>
<td>$AUC_{0-24h}$ (CV%) mg*h/L</td>
<td>49.3 (77)</td>
<td>77.0 (22)</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (CV%) mg/L</td>
<td>5.4 (50)</td>
<td>8.0 (22)</td>
</tr>
</tbody>
</table>

PK expressed as geometric mean with coefficient of variation (%), and median (range) for dose/weight. FCT, film-coated tab; DT, dispersible tab

\textsuperscript{a}Fasted HIV-positive adults. \textsuperscript{b}HIV-positive treatment experienced adults, fed state not specified.

- $C_{\text{trough}}$ low in 6–<10kg weight band
- $AUC$ in between adult QD and BID
- $C_{\text{max}}$ somewhat higher than adult in higher weight bands (10–<20)
**Children- WHO 2018 Recommendations and Guidance**

**Simplify and optimize diagnostics**

**Move away from NNRTI-based regimens**

**Introduce DTG as soon as possible**

**Use the most potent non-NNRTI option**

<table>
<thead>
<tr>
<th></th>
<th>NEONATES</th>
<th>CHILDREN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preferred</strong></td>
<td>AZT+3TC+RAL&lt;sup&gt;1&lt;/sup&gt;</td>
<td>ABC+3TC+DTG&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Alternatives</strong></td>
<td>AZT+3TC+NVP&lt;sup&gt;3&lt;/sup&gt;</td>
<td>ABC+3TC+LPV/r&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Only age &lt;2 wks</td>
<td>ABC+3TC+RAL&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>ABC (or AZT)+3TC+EFV</td>
<td>ABC (or AZT)+3TC+RAL&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>AZT+3TC+LPV/r</td>
<td>AZT+3TC+LPV/r</td>
</tr>
<tr>
<td></td>
<td>AZT+3TC+RAL</td>
<td>AZT+3TC+RAL</td>
</tr>
<tr>
<td></td>
<td>AZT+3TC+NVP</td>
<td>AZT+3TC+NVP</td>
</tr>
</tbody>
</table>

<sup>1</sup> For the shortest time possible, until a solid formulation of LPV/r or DTG can be used
<sup>2</sup> For age and weight groups with DTG approved dosing (50 mg adult tablet from 20 kg TLD can be used in adolescents weighting more than 30 kg)
<sup>3</sup> In cases where no other alternatives are available
Children - Transition to Optimal Regimens

### Goal of transition
- Improve outcomes
- Harmonization
- Simplification
- Supply security

### Children eligible for transition
- Already on ART
- Clinically stable (defined as per national guidelines)
- Prioritize children on NNRTI based regimen

### Current regimen | Weight | Optimal regimen for transition | Considerations
--- | --- | --- | ---
AZT/3TC/NVP AZT/3TC/EFV ABC/3TC/NVP | <20 kg | ABC/3TC/LPVr | If still stable these can be transitioned to DTG when they reach 20 kg
| 20-30kg | ABC/3TC/DTG | If still stable these can be transitioned to TLD when they reach 30 kg
| > 30kg | TLD | - |
ABC/3TC/EFV | <20 kg | No change until reach 20 kg unless treatment failure occurs | Of value once reached 20 kg when DTG can be used so that OD administration is preserved.
| 20-30kg | ABC/3TC/DTG | If still stable these can be transitioned to TLD when they reach 30 kg
| > 30kg | TLD | - |
ABC/3TC/LPVr AZT/3TC/LPVr | <20 kg | No change until reach 20 kg unless treatment failure occurs | Important to ensure use of tablets as soon as possible to reduce pill burden. Transition from AZT/3TC/LPVr to ABC/3TC/LPVr can also be considered to reduce pill burden
| 20-30kg | ABC/3TC/DTG | If still stable these can be transitioned to TLD when they reach 30 kg
| > 30kg | TLD | - |
Safety and Efficacy of E/C/F/TAF in Virally Suppressed Children Through 96 Weeks

Rakhamanina N et al. Pediatric HIV Workshop, July 2019, Mexico City, Abs. 22

- **Switch study in virally suppressed children on ART.**
  - Phase 2/3 open-label, multicohort, switch study conducted in USA, Uganda and Thailand
  - HIV-1-infected children (6 – <12 y; ≥25 kg)
    - Suppressed on stable ART (HIV-1 RNA <50 c/mL for ≥6 mo)
    - CD4 count >100 cells/μL
    - eGFR (Schwartz formula) ≥90 mL/min/1.73m²

- **PK consistent with prior studies; viral efficacy maintained.**
  - TAF, TFV exposures generally higher than adults but within ranges of E/C/F/TAF & B/F/TAF programs
    - 52% higher TAF AUC_{tau}
    - 45% higher TFV AUC_{tau}; 53% higher TFV C_{max}
  - EVG, COBI, FTC exposures (noncompartmental analysis) within range of historical data associated with long-term safety, efficacy in E/C/F/TDF and E/C/F/TAF-treated adults and pediatrics

- **No Gr ≥3 AE or SAE or AE leading to drug dc.** No renal AE and bone z-score consistent with age reference population.
Drug Resistance Mutations in Youth Failing ART
Kouamou V.  IAS July 2019, Mexico City  Abs. WEAB0203

- Evaluated presence of drug resistance mutations (DRM) in cohort of 160 children age 10-24 yrs (median 18 yr) with viral failure 1\textsuperscript{st} line (N=112) or 2\textsuperscript{nd} line (n=48) ART enrolled in peer support intervention.
- 86% had $\geq 1$ DRM
- Dual resistance to NRTIs and NNRTIs detected in 96 (60%) 1\textsuperscript{st} line failures.
- PI resistance uncommon in 2\textsuperscript{nd} line failures.

→ Switch of 1\textsuperscript{st} line failure to TLD may be problematic given K65R and M184V frequent. Drug resistance data is needed to inform strategies for implementation of TLD as 2\textsuperscript{nd} and 3\textsuperscript{rd} line ART.
Summary

- DTG recommended by WHO as preferred 1st line for all children >20kg.
- Dosing for younger age groups/lower weight bands underway; dispersible tablet preparation may be available for children 6-20 kg in near future.
- E/C/F/TAF appears safe and effective in older children who are virally suppressed.
- Dual NRTI and NNRTI drug resistance mutations frequent in children failing 1st line ART which may complicate transition to more optimal regimens.
Adolescents and HIV, Including PrEP in Adolescents and Women
High Incidence of HIV Acquisition Among Young Women in ECHO Trial, South Africa

Palanee-Phillips T et al. IAS July 2019, Mexico City, Abs. LBPEC23

- ECHO trial evaluated HIV incidence among sexually active HIV-negative women 15-49 yrs randomized to DMPA, LNG implant or copper IUD contraception; no difference found.
- This analysis focused on 5,768 women enrolled in South Africa, median age 23 years (63% ≤24 yr), with 7,647 women-years (WY) follow-up.
- 345 infections for incidence of 4.51 (95% CI 4.1-5.0) per 100 W-Y.
- Age ≤24 yr, baseline STI, BMI <30, and new/multiple partners associated with HIV acquisition.

<table>
<thead>
<tr>
<th>Site</th>
<th>Enrolled (n)</th>
<th>HIV seroconversions (n)</th>
<th>Woman-years of follow-up</th>
<th>HIV incidence per 100 woman-years</th>
<th>Lower bound</th>
<th>Upper bound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brits</td>
<td>407</td>
<td>18</td>
<td>544.83</td>
<td>3.30</td>
<td>1.96</td>
<td>5.22</td>
</tr>
<tr>
<td>Cape Town</td>
<td>560</td>
<td>31</td>
<td>703.82</td>
<td>4.40</td>
<td>2.99</td>
<td>6.25</td>
</tr>
<tr>
<td>Durban</td>
<td>861</td>
<td>52</td>
<td>1172.24</td>
<td>4.44</td>
<td>3.31</td>
<td>5.82</td>
</tr>
<tr>
<td>East London</td>
<td>614</td>
<td>44</td>
<td>819.45</td>
<td>5.37</td>
<td>3.90</td>
<td>7.21</td>
</tr>
<tr>
<td>Edendale</td>
<td>611</td>
<td>40</td>
<td>825.71</td>
<td>4.84</td>
<td>3.46</td>
<td>6.60</td>
</tr>
<tr>
<td>Johannesburg</td>
<td>697</td>
<td>28</td>
<td>923.62</td>
<td>3.03</td>
<td>2.01</td>
<td>4.38</td>
</tr>
<tr>
<td>Klerksdorp</td>
<td>555</td>
<td>39</td>
<td>759.10</td>
<td>5.14</td>
<td>3.65</td>
<td>7.02</td>
</tr>
<tr>
<td>Ladysmith</td>
<td>653</td>
<td>56</td>
<td>823.13</td>
<td>6.80</td>
<td>5.14</td>
<td>8.84</td>
</tr>
<tr>
<td>Soshanguve</td>
<td>810</td>
<td>37</td>
<td>1074.90</td>
<td>3.44</td>
<td>2.42</td>
<td>4.75</td>
</tr>
</tbody>
</table>
Comparison LAg avidity EIA assay to Asante Rapid Test for Recent Infection (RTRI) found 95% agreement when VL included in recent infection surveillance pilot.

Age difference by sex in recent infections
Recent infections in ~ 1 in 5 HIV infections diagnosed in males 20-24 years and in females 13-19 years

Highest rate recent infections: in-pt, ANC and dermatology clinic, followed by STI and VCT
Recent Infection Surveillance Among Pregnant Adolescent Girls and Young Women in Malawi

Nyirenda R. July 2019, Mexico City  Satellite Recency Testing

- Cross-sectional estimate of HIV incidence in AGYW attending their 1st ANC visit in public facilities newly diagnosed with HIV in Malawi using recency infection testing algorithm (RITA) with Limiting Antigen Avidity (LAg) assay.

<table>
<thead>
<tr>
<th>District</th>
<th>N</th>
<th>#</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blantyre</td>
<td>184</td>
<td>22</td>
<td>12.0</td>
</tr>
<tr>
<td>Lilongwe</td>
<td>224</td>
<td>32</td>
<td>14.3</td>
</tr>
<tr>
<td>Machinga</td>
<td>83</td>
<td>9</td>
<td>10.8</td>
</tr>
<tr>
<td>Zomba</td>
<td>98</td>
<td>5</td>
<td>5.1</td>
</tr>
<tr>
<td>Total</td>
<td>589</td>
<td>68</td>
<td>11.7</td>
</tr>
</tbody>
</table>

- About 1 in 10 newly diagnosed pregnant AGYW at ANC were recently infected.
- Proportion of recent infections was lower in Zomba than other districts.
- Results indicated that AGYW were not being tested frequently/early enough.

Estimated annual incidence in pregnant AGYW 0.59%
- Higher in 20-24 yr/o AGYW
- Differs by district
Predictors of HIV Incidence in Adolescent Girls, Malawi

Kudowa E et al. IAS July 2019, Mexico City Abs. MOPE324

- Prospective cohort 795 sexually active adolescent girls 15-24 yr at 4 centers Lilongwe Malawi 2016-2017; evaluated risk assessment tool and correlated with HIV acquisition.

- 14 infection/672 PY = incidence 2.08/100 PY (95% CI 1.2-3.5).

- Risk tool had 4 variables and 5 points; score ≥3 had HIV incidence 5.88/100 PY – sensitivity 64%, specificity 76%.

<table>
<thead>
<tr>
<th>Variable</th>
<th>aIRR</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal discharge</td>
<td>2.61 (0.84, 8.09)</td>
<td>No=0, Yes=1</td>
</tr>
<tr>
<td>Genital ulcer</td>
<td>1.94 (0.57, 6.62)</td>
<td>No=0, Yes=1</td>
</tr>
<tr>
<td>Ever pregnant</td>
<td>4.55 (1.23, 16.85)</td>
<td>No=0, Yes=2</td>
</tr>
<tr>
<td>Partner &gt;5 yr older</td>
<td>2.42 (0.77, 7.56)</td>
<td>No=0, Yes=1</td>
</tr>
</tbody>
</table>

Risk Score Value and HIV Incidence/100 PY

aIRR: adjusted incidence rate ratio
Financial Incentives to Reduce HIV Incidence Among Adolescent Girls and Young Women

Gorgens M et al. IAS July 2019, Mexico City Abs. TUAC0205LB

- From Nov 2015 – March 2016, enrolled 4,389 adolescent girls and young women (AGYW) aged 15-22 in Eswatini from 266 non-overlapping areas (map)
- Stratified enrolment: in school or out of school (50:50); rural vs urban (80:20)
- 2x2 factorial design: education incentive only; raffle incentive only; both; none

**EDUCATION INCENTIVE**
- Paid for enrolling in & attending school (E1400 [~$100]/yr)
- Paid for enrolling in & completing other education like tertiary education/upgrading/short course (E1400 [~$100]/yr)
- Only in 2018, tuition fees paid for out of school participants (up to E2900 (~$200) per course)

**RAFFLE INCENTIVE**
- 50% of participants also eligible for raffle. 7 raffles held
- Each raffle round, 400 randomly selected for STI testing
- If negative for *syphilis* and *trichomonas vaginalis*, then eligible for raffle prize
- 80 raffle winners every round, 560 raffle winners in total (raffle prize money per round: E1000 [~$72])

Timeline

- Baseline: November 2015
- Midline: May to August 2017
- Endline: November 2018

Raffle Interventions

- Round 1 to Round 7
- Raffle prize money per round: E1000 [~$72]
Financial Incentives to Reduce HIV Incidence Among Adolescent Girls and Young Women
Gorgens M et al. IAS July 2019, Mexico City Abs. TUAC0205LB

- From Nov 2015 – March 2016, enrolled 4,389 adolescent girls and young women (AGYW) aged 15-22 in Eswatini from 266 enumerator areas
- Stratified enrolment: in school or out of school (50:50); rural vs urban (80:20)
- 2x2 factorial design: education incentive, raffle incentive, both, none; endpoint HIV incidence

**EDUCATION INCENTIVE**
- 52% got prizes
  - 52% of participants enrolling in & attending school (E1400 [~$100]/yr)
  - 31% of participants enrolling in & completing other education like tertiary education/upgrading/short course (E1400 [~$100]/yr)
  - 2018, tuition fees paid for out of school participants (up to E2900 (~$200) per course)

**RAFFLE INCENTIVE**
- 19% got prizes
  - 50% of participants also eligible for raffle. 7 raffles held.
  - 400 randomly selected for STI testing
  - If negative for *syphilis* and *trichomonas vaginalis*, then eligible for raffle prize
  - 80 raffle winners every round, 560 raffle winners in total (raffle prize money per round: E1000 [~$72])

**3-Yr HIV Incidence**
- End-line Evaluation: 86% overall
# Financial Incentives to Reduce HIV Incidence Among Adolescent Girls and Young Women

Gorgens M et al. IAS July 2019, Mexico City Abs. TUAC0205LB

<table>
<thead>
<tr>
<th>Arms</th>
<th>HIV incidence</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adjusted for raffle incentive</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No education control arms</td>
<td>8.1%</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Education arm</td>
<td>6.3%</td>
<td>0.77 (0.60-0.98)</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Adjusted for education incentive</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No raffle control arms</td>
<td>7.8%</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Raffle arm</td>
<td>6.6%</td>
<td>0.83 (0.65-1.07)</td>
<td>0.15</td>
</tr>
</tbody>
</table>

**HIV incidence ↓23% in education arm vs no education arms over 3-year study**

**No effect raffle arm vs no raffle arms**

<table>
<thead>
<tr>
<th>2x2 factorial analysis</th>
<th>HIV incidence</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No intervention</td>
<td>8.8%</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Raffle only</td>
<td>7.4%</td>
<td>0.82 (0.59, 1.14)</td>
<td>0.245</td>
</tr>
<tr>
<td>Education only</td>
<td>6.9%</td>
<td>0.76 (0.54-1.07)</td>
<td>0.116</td>
</tr>
<tr>
<td>Education and raffle</td>
<td>5.8%</td>
<td>0.63 (0.44, 0.91)</td>
<td>0.013</td>
</tr>
</tbody>
</table>

**HIV incidence 37% less likely with education plus raffle arms vs no intervention over 3-year study**
Financial Incentives to Reduce HIV Incidence Among Adolescent Girls and Young Women

Gorgens M et al. IAS July 2019, Mexico City Abs. TUAC0205LB

For each additional round of education incentive received, HIV incidence over 3 years was reduced by 3.9 percentage points (p=0.014)

→ Out of school, more risky decisions: ↑ risk
→ Higher education, less poverty: ↓ risk

Profile of Participant | How Likely to Have Acquired HIV
--- | ---
Being out of school | 190% more likely to have acquired HIV
‘Risk-loving’ participants* | 145% more likely to acquire HIV
At education level years 1-5 | 56% less likely to have acquired HIV
Richest 20% of participants | 35% less likely to acquire HIV
At education level Forms 1-6 | 29% less likely to have acquired HIV

* ‘Risk-loving’ participants: during surveys, played a game with participants to assess their propensity to take risk when it comes to financial decision making. Based on how they responded, participants were classified on a scale ranging from risk averse to risk loving.
Lessons Learned: Menu of Strategies Needed to Target Young People at Risk
Mullick S. IAS July 2019, Mexico City Satellite MOSA09

### Project PrEP – collaboration with S Africa MoH to integrate PrEP into comprehensive sexual and reproductive health services for girls in 3 provinces S Africa.

#### Implementation Model

**“Hotspot” mapping with mix of clinic and mobile van outreach**

**Resourcing**
- **Utilising existing NIMART trained nurse in clinic and other trained staff to provide PrEP to AGYW**
- **Capacity building and mentorship of providers throughout the project**
- **Assisting facility to create youth friendly zones and provide youth friendly SRH and HIV services**
- **Roving unit equipped with NIMART nurse, counsellor and data capturer**
- **Provided one data collection clerk per clinic to support enhanced monitoring activities**

**Know Your Population:** Menu strategies needed at each level

#### Minimum Clinical Package – More Than Just PrEP

<table>
<thead>
<tr>
<th>Cluster</th>
<th>Services rendered through the Mobile Van</th>
<th>Services rendered in the fixed facility</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mthatha</td>
<td>HIV testing&lt;br&gt; Syriotic STI diagnosis and Rx&lt;br&gt; PrEP Screening and initiation&lt;br&gt; TB screening&lt;br&gt; PEP&lt;br&gt; Pregnancy test&lt;br&gt; Contraception/Family planning&lt;br&gt; Counselling (screening for mental health, alcohol/substance use/mental health&lt;br&gt; Condoms&lt;br&gt; Pregnancy test - links for ANC and abortion services&lt;br&gt; Mental health services&lt;br&gt; IPV/GiV services</td>
<td>All services provided on the mobile and the mobile refers for services below</td>
<td>All referral cases are attended at the facility. There are weekly meetings between the facilities and the mobile clinic teams to discuss among others referrals.</td>
</tr>
<tr>
<td>Port Elizabeth</td>
<td></td>
<td></td>
<td>Reporting of GiV seems rare, a mobile clinic nurse screens and refers to the specialist at the fixed facility/CBO.</td>
</tr>
<tr>
<td>eThekwini</td>
<td>Laboratory STI diagnosis&lt;br&gt; Hep B screening &amp; vaccination&lt;br&gt; Pregnancy test - links for ANC and abortion services&lt;br&gt; Mental health services&lt;br&gt; IPV/GiV services&lt;br&gt; Alcohol/substance use services&lt;br&gt; Cervical cancer screening and HPV</td>
<td></td>
<td>The reporting of mental health cases also seem rare, which is not necessarily an accurate reflection - where identified, cases are referred to a psychiatric nurse.</td>
</tr>
<tr>
<td>Tshwane</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Combination Strategies Needed

Both clinics and mobile vans needed

- **Strategically mapped hotspots to access AGYW**
- **Hotspot visits at academic institutions such as TVETS, Universities, Colleges, high schools reaches target group and appropriate age**
- **Extended working hours and Conduct hotspot visits on weekends.**

**Strategies used to identify PrEP clients at the hotspots**
- Reached AGYW at winter schools where available.
- Mobile clinic convenient for AGYW - opportunity to build good rapport, trust and confidence with mobile clinic teams - same professional nurse and her/his team servicing AGYW while facilities staff are inconsistent.

**Strategies used to identify PrEP clients at the fixed facilities**
- Ensuring continuity at fixed facility - PrEP nurse always available for initiation encourages AGYW to access facility services.
- Ensuring presence of youth friendly nurse champions at facilities to promote youth friendliness - increase in number of AGYW visits.
As in Other Studies, PrEP Initiation Good, But Retention/Adherence Poor

As in Other Studies, PrEP Initiation Good, But Retention/Adherence Poor

A Menu of Options is Needed to Assist Adherence

Lessons Learned: Menu of Strategies Needed to Target Young People at Risk
Mullick S. IAS July 2019, Mexico City Satellite MOSA09

AGYW Need More Than Just PrEP

<table>
<thead>
<tr>
<th>AGYW partners average 4+ yr older</th>
<th>24% report partner 5-10 yr older</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-37% ever pregnant</td>
<td></td>
</tr>
<tr>
<td>4-12% treated for an STI in the last 3 mos</td>
<td></td>
</tr>
<tr>
<td>3-18% ever had a pap smear</td>
<td></td>
</tr>
<tr>
<td>42-61% not tested for HIV in the last 3 months</td>
<td></td>
</tr>
<tr>
<td>2-12% had a partner physically hurt them</td>
<td></td>
</tr>
<tr>
<td>32-56% report low on energy, depressed or hopeless</td>
<td></td>
</tr>
<tr>
<td>17-55% report feeling bad about yourself</td>
<td></td>
</tr>
</tbody>
</table>

Lessons Learned: Menu of Strategies Needed to Target Young People at Risk
Mullick S. IAS July 2019, Mexico City Satellite MOSA09

A Menu of Options is Needed to Assist Adherence

Reason for Discontinuation of PrEP

- Long school holidays with no access to a facility
- Lack of support from parents/guardians to AGYW
- AGYW are not comfortable with community members seeing them at fixed facilities

Strategies to address the gaps

- Provide PrEP supply to last during holiday periods - Refer to www.myprea.co.za/locations to access PrEP from their nearest PrEP providing health centre
- Continue with parent/caregiver/community dialogues on oral PrEP to encourage support for AGYW taking up PrEP and continuing
- Offer them an option to visit the mobile clinic

Strategies used to retain PrEP clients

- Peer support through social media such as WhatsApp groups, e.g. a facility in KZN set up PrEP WhatsApp group for all AGYW who are taking PrEP
- Frequent contact with client on PrEP especially trained counsellors to provide detailed counseling to PrEP clients
- Behavioural counseling and regular follow up through the telephone, e.g. in Gauteng, the lay counsellor does this regularly
- Facilitate decision making by client e.g. service provider would ask client (AGYW) “when would you like to come back” and help them to cope with the need for frequent follow up

Youth NEED MORE THAN JUST PrEP – Importance of Service Integration

Integrate oral PrEP into other SRH services e.g. STI management and Family Planning

Ensure that nurses are trained on NIMART, oral PrEP and how to integrate services

Provide a mobile clinic van which is a one-stop shop service points of oral PrEP and SRH

Establish youth clinic that provides comprehensive health care services including SRH & PrEP

Ensure constant communication with facility teams through quarterly meetings to reinforce the importance and advantages of integration of services

Establish strong referral network within and beyond facility in circumstances where you do not have adequate trained personnel
Characteristics and Long-Term Outcomes of Youth with Perinatal HIV in IeDEA Southern Africa Collaboration

Tsondai P et al. IAS July 2019, Mexico City Abs. WEAB0201

- 25,126 youth in care at 15 IeDEA-SA sites in 6 countries 2004-2017, perinatal infection, had ≥1 visit between age 10-19 yrs

Children with perinatal HIV have suboptimal retention, viral suppression and survival during adolescence. Those initiating ART at older ages and those immunosuppressed during adolescence need careful follow-up to optimize outcomes.

- 89% on an NNRTI-based regimen
- ~ 55% had weight and height measures
  - 38% stunted (HAZ < -2)
  - 27% underweight (WAZ < -2)
- Among those in care within sites with routine VL testing (n=7331)
  - 73% had a VL measure
  - 78% had a VL ≤ 400 copies/mL
PrEP Use in Young African Women, HPTN 082
Effect of Drug Level Feedback

Celum C et al. IAS July 2019, Mexico City Abs. TUAC0301

- High PrEP initial uptake - 95% overall (88-99% sites)
- Adherence declines after 3 mos (change to quarterly visits)

<table>
<thead>
<tr>
<th></th>
<th>3 mos</th>
<th>6 mos</th>
<th>12 mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir diphosphate (TFV-DP), DBS</td>
<td>N=371</td>
<td>N=363</td>
<td>N=347</td>
</tr>
<tr>
<td>Detectable</td>
<td>83.6%</td>
<td>56.5%</td>
<td>31.4%</td>
</tr>
<tr>
<td>&gt;700 fmol/punch* (in those with detectable TFV-DP)</td>
<td>24.8%</td>
<td>20.9%</td>
<td>8.6%</td>
</tr>
</tbody>
</table>

- No effect of (delayed) drug level feedback: TDF-DP >700 fmol at 6 month
  - 21.7% SOC vs 20.1% feedback
<table>
<thead>
<tr>
<th>Covariate</th>
<th>Univariate Odds Ratio (95% CI)</th>
<th>Multivariate Odds Ratio (95% CI)</th>
<th>Multivariate P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perceived risk of HIV (any vs none)</td>
<td>1.9 (1.1, 3.2)</td>
<td>2.4 (1.2, 4.5)</td>
<td>0.008</td>
</tr>
<tr>
<td>PrEP readiness score (per unit increase)</td>
<td>1.0 (1.0, 1.1)</td>
<td>1.0 (1.0, 1.1)</td>
<td>0.004</td>
</tr>
<tr>
<td>Disclosed to someone about PrEP use</td>
<td>3.3 (1.2, 8.8)</td>
<td>3.0 (1.0, 9.1)</td>
<td>0.06</td>
</tr>
<tr>
<td>Number of sexual partners, past 3 months</td>
<td>1.2 (1.0, 1.5)</td>
<td>1.3 (1.0, 1.6)</td>
<td>0.07</td>
</tr>
<tr>
<td>Participant ever dropped out of school</td>
<td>1.8 (1.0, 13.1)</td>
<td>2.0 (1.0, 14.1)</td>
<td>0.07</td>
</tr>
<tr>
<td>Adherence club participation (club attendance)</td>
<td>1.7 (1.2, 2.3)</td>
<td>1.3 (1.0, 1.8)</td>
<td>0.10</td>
</tr>
</tbody>
</table>

- Four HIV sero-converters (at mos 3, 6, and two at 9) observed in 404 person-years FU; HIV incidence of 1.0/100 person-years (95% CI 0.3-2.5) (low considering risk profile).
- Seroconversion due to non-adherence: 2 had undetectable DBS TFV-DP concentrations and 2 detectable but low concentrations (74 and 243 fmol/punch) in the visit at or prior to when they were first detected HIV seropositive.
PrEP Adherence in Young Women Initiating PrEP in Maternal-Child Health or Family Planning Clinics: PrIYA Program, Kenya

Pintye J et al. IAS July 2019, Mexico City Abs. TUAC0305LB

- 22% acceptance, with 40% continuing at 1-month.
- July 2018 randomly selected DBS from 20% FU visits where woman reported using PrEP in last 14 days (and one sero-converter).

<table>
<thead>
<tr>
<th>Median time since PrEP initiation</th>
<th>Frequency of detectable TFV-DP</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 weeks (IQR 4-18)</td>
<td>62%</td>
</tr>
<tr>
<td>24 weeks (IQR 17-37)</td>
<td>90%</td>
</tr>
<tr>
<td>None detected</td>
<td></td>
</tr>
</tbody>
</table>

PrEP adherence more likely in older, non-pregnant women and highest in women with known HIV+ partner.

Factors Associated with Detectable TFV-DP

<table>
<thead>
<tr>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.4 (1.1-1.5)</td>
</tr>
<tr>
<td>1.3 (1.0-1.8)</td>
</tr>
<tr>
<td>2.6 (1.7-3.4)</td>
</tr>
<tr>
<td>1.6 (1.1-2.3)</td>
</tr>
</tbody>
</table>
PrEP Reinitiation After Interruption by Adolescent Girls and Young Women in Kenya and South Africa
Omollo V et al. IAS July 2019, Mexico City Abs. TUAC0304

- POWER is a PrEP project among AGYW ages 16-25 in Kisumu, Kenya, Johannesburg and Cape Town, South Africa; AGYW are offered PrEP, visits at mo 1 and then quarterly.
- Patterns of PrEP use measured using pharmacy records; PrEP interruption was defined as PrEP not dispensed at a visit or a gap of >14 days without PrEP due to a missed visit.
- PrEP uptake was high: June 2017-November 2018, enrolled 1367 AGYW (median age 20 yr); 92% (1254) accepted PrEP.
- PrEP interruptions were common: of 970 women with 6 mo FU after PrEP start, 95% (917) had a PrEP interruption; most (874/917, 95%) were due to late or missed visits.
- PrEP re-initiation in 25%: Of 644 women who could have had 6 mo FU after an interruption, 25% (160) re-initiated PrEP within a mo of interruption in 59% (median 38 d).
- PrEP interruption was often intentional: Women reported travel and relationship dissolution and sexual abstinence as reasons for interruptions.
Summary

- High incidence of HIV acquisition in young girls continues to be documented; risk factors (STI, pregnancy, older partner).
- Multi-component interventions are required for HIV prevention in young people.
- Financial incentives effective in some decrease (23-37%) incidence in one study; cost-effectiveness evaluation being done.
- Adolescents with perinatal HIV need special attention to retention, ART adherence and viral suppression as long-term outcome suboptimal.
- While high PrEP uptake by adolescent girls/young women, retention to PrEP remains a problem and additional and more frequent support is needed.
TB and HIV

- Pregnancy
- Pediatrics
High IPT Use in HIV+ Pregnant Women, Kenya
LaCourse SM et al. IAS July 2019, Mexico City Abs. TUBEB157

- Observational study of IPT use in pregnancy nested within an Infant TB Infection Prevention Study (iTIPS) in western Kenya, 2016-2018.
- 300 HIV+ mothers enrolled at 4 sites at 6-10 wks postpartum, all on ART; questionnaire re: IPT use in pregnancy – 75% (224) report use of IPT, with 92% reporting completing 6 mo.

Cumulative IPT Use in HIV+ Women
Timing of IPT Use and Pregnancy

Correlates of IPT Use in HIV+ Women

- >50% of initiated during pregnancy/early postpartum, of which 46% initiated during 1st trimester
Factors Influencing Adherence to IPT in Infants in iTIPS Trial, Kenya

Black D et al. IAS July 2019, Mexico City Abs. TuPEC459

- Ongoing RCT in 300 HIV-exposed uninfected infants randomized at age 6 wk to 12 mo IPT vs no IPT (Infant TB Infection Prevention Study, iTIPS); FU ongoing.

- Assessed adherence by maternal report in IPT arm and associated factors.

- Among 135 mother-infant pairs in IPT arm at 6 mo FU, 18% missed a dose in last week; among these 29% also missed dose in last month,

- Comparing adherent and non-adherent mothers, adherence associated with:
  - Prior maternal TB dx (14% vs 0%, p=0.04)
  - Initiation ART prior to pregnancy vs during/early PP (79% vs 54%, p=0.01)
Data from 22,490 children 0-18 years from 2013-2017 from EMR and national registers at 7 Baylor BIPAI Centers Excellence. Facility-based TB screening is done at each site.

- 96% completed TB screening
- 58% had + TB screen at ≥1 visit
- After clinical evaluation, 41% with + screen classified as presumptive TB
- 27% of presumptive TB cases diagnosed with TB (32% confirmed cases)
- TB treatment started in 84% with TB
- 74% completed treatment/cured.

**TB disease is confirmed in 32% of patients who begin ATT**

16% didn't start TB rx
26% didn’t complete
Summary

▪ Frequent use of preconception IPT, although limited data in pregnancy.
▪ Adherence to IPT in infants (like ARVs) difficult and specific support to develop strategies to assist adherence would help.
▪ TB cascade in children (like 90-90-90 cascade) is suboptimal even at Centers of Excellence sites.
ART in Women

The Future: New Drugs
ADVANCE Trial: DTG/F/TAF vs DTG/F/TDF vs EFV/F/TDF

Venter F et al. IAS July 2019, Mexico City Abs. WEAB0405LB

DTG non-inferior to EFV

Efficacy: Proportion with RNA <50 by Arm (ITT)

Resistance uncommon with failure

<table>
<thead>
<tr>
<th></th>
<th>TAF/FTC+DTG (n=351)</th>
<th>TDF/FTC+DTG (n=351)</th>
<th>TDF/FTC/EFV (n=351)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number w/VF, tested for resistance with paired baseline genotype</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
<td>6 (2%)</td>
</tr>
<tr>
<td>Emergent NNRTI mutation</td>
<td>0 (0%)</td>
<td>0 (0.3%)</td>
<td>4 (1%)</td>
</tr>
<tr>
<td>Emergent NRTI mutation</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Emergent INSTI mutation</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Toxicity low

- DEXA better with TAF (osteopenia hip 7% TAF vs 16-18% TDF; spine 18% vs 22-23%)
- Renal better with TAF (Gr ≥3 ClCr 1% TAF vs 2-4% TDF)
- More d/c due to EFV-related AE, 8 (2.3%) vs 1 DTG-TAF, 0 DTG-TDF

Viral failure and resuppression:

- DTG-TAF: 18; 15 resuppressed on DTG-TAF (1 no FU)
- DTG-TDF: 19; 14 resuppressed on DTG-TDF (2 no FU)
- EFV-TDF: 16; 7 resuppressed on EFV-TDF (2 no FU)

Treatment differences (90.3% CI)

- Non-inferiority margins used for the single zeroes analyses n=10%

DTG-TAF vs DTG-TDF

DTG-TDF vs EFV-TDF

DTG-TAF vs EFV-TDF

Mean change weight: MEN

Wilcoxon rank-sum comparison at Week 96:

- n.s. not significant
- * p<0.05, ** p<0.01, *** p<0.001

Mean change weight: WOMEN

Wilcoxon rank-sum comparison at Week 96:

- * p<0.05, ** p<0.01, *** p<0.001

96 Weeks

1053 Adults 59% ♀

- ART naïve
- RNA >500
- No TB or pregnancy
96-Week Efficacy and Safety of Switching to BIC//TAF in Women

Kitya C. IAS July 2019, Mexico City Abs. MOAB0106

- 470 HIV+ women suppressed on EVG (E/C/F/TAF or E/C/F/TAF) or ATV/r/F/TDF >6 mos and eGFR≥50 mL/min randomized to B/F/TAF or stay on regimen (switch at 48 wks)

**Resistance:**
- No emergent resistance among 4 with viral failure RNA >200 c/m
- 1 pt (SBR E/C/F/TAF) developed M184V at wk 48, suppressed on B/F/TAF

**Viral suppression:**
- Sustained viral suppression on B/F/TAF 96 wk or after switch at 48 wk

**Toxicity:**
- Low frequencies of grade 3 or 4 AEs (6.7%), treatment-related AEs (5.8%), or serious AEs (5.2%).
- 1 pt who got B/F/TAF in extension phase d/c treatment due to drug-related AEs (grade 2 elevated ALT, AST, and GGT).

**Pregnancy on B/F/TAF**
(stopped drug if pregnant)

<table>
<thead>
<tr>
<th>Group</th>
<th>Participants, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A+B</td>
<td>All B/F/TAF</td>
</tr>
<tr>
<td></td>
<td>N=462</td>
</tr>
<tr>
<td></td>
<td>Confirmed pregnancy</td>
</tr>
<tr>
<td></td>
<td>Live birth*</td>
</tr>
<tr>
<td></td>
<td>Fetal death*</td>
</tr>
<tr>
<td></td>
<td>Elective abortion</td>
</tr>
<tr>
<td></td>
<td>Pregnancy outcome unknown†</td>
</tr>
</tbody>
</table>

* 1 live birth of infant with patent urachus, requiring no intervention and was absent on repeat ultrasound.† twin pregnancy that resulted in fetal deaths: 1 in utero and 1 stillbirth; both fetal deaths were reported as SAEs and were not attributed to study drug.† Participants were lost to follow-up.
New Drugs: MK-8501, Ilatravir (ISL) for Treatment or Prophylaxis  
IAS July 2019, Mexico City

**MK-8501 (Ilatravir):** nucleoside reverse transcriptase translocation inhibitor (NRTTI)

- Ilatravir, a First-in-Class NRTTI with Multiple Mechanisms of Action

  * Prevents nucleotide binding and incorporation to the DNA chain, resulting in immediate chain termination.

  * Prevents nucleotide incorporation even in the event of translocation. Ilatravir is no longer susceptible to resistance-conferring mutations once out of the active site.

**Molina, LBPED46:** N=121, phase IIB ISL doses 0.25, 0.75, or 2.25 mg with DOR and 3TC (vs DOR/3TC/TDF). No SAE, drug d/c, resistance.

Week 24 VL <50:

- 90% ISL 0.25/3TC/TDF
- 100% ISL 0.75/3TC/TDF
- 87% ISL 2.25/3TC/TDF
- 87% DOR/3TC/TDF

**Molina, WEAB0402LB:** Suppressed on triple x24 wk, switch to ISL/DOR to 48 wk. Dual no SAE, drug dc, resistance.

Week 48 VL <50:

- 90% ISL 0.25/3TC/TDF
- 90% ISL 0.75/3TC/TDF
- 78% ISL 2.25/3TC/TDF
- 84% DOR/3TC/TDF

**Matthews, TUAC0401LB:** Phase 1 implant (54 or 62 mg). Projected ISL-TP levels adequate for prophylaxis for at least a year

- Long IC T½: 120 hr
- Potential for daily, once wk or less frequent dosing
- Potent against NRTI resistant virus

**Projected C_{max} ISL-TP:** 0.07 pmol/10^6 cells

**Projected PK Threshold:** 0.05 pmol/10^6 cells

**XRCT of ISL implant**

**Mean Observed Plasma Data Model fit**
Fostemsavir (FTR) first in-class attachment inhibitor prodrug of temsavir (TMR).

BRIGHTE phase 3 study in heavily ART-experienced patients with multi-drug resistant HIV.

Advanced disease: CD4 80 (RC, 100; NCT, 41); 86% AIDS

In RC, week 96, 60% had viral suppression, mean $\uparrow$ CD4 240 cells; 67% with baseline CD4 $<200 \uparrow$ to $>200$; 56% with $<50 \uparrow$ to $>200$

Higher SAEs, Gr $\geq 3$ AE and death in the Non-RC (48%/49%16%) vs. RC (34%/29%/4%). Overall, 38% had an SAE; 3% were drug related. 7% dc due to AE.
GS-6207 is novel, long-acting inhibitor of HIV capsid function with picomolar activity all HIV subtypes.

- Single subcutaneous dose maintained systemic exposure for $\geq 24$ weeks.

- Phase Ib placebo-controlled study (3:1 randomization, N-8/group) ART naïve received single-dose 20-50-150-450-750 mg vs placebo, evaluating VL reduction through day 10 (day 10 all started B/F/TAF).

- 1.8-2.2 log dose-related ↓RNA; no SAE (mild injection site reaction 63%).
The Future:

New PrEP Options
Update on Long-Acting PrEP

Cohen M. IAS July 2019, Mexico City Symposium MOSY05

HPTN 083/084: Evaluating safety and efficacy of CAB LA vs TDF/FTC for prevention

- 3 protocols (one MSM/TG, one women) comparing injection CAB-LA vs oral TDF for prevention HIV over 3.5 years.
- Enrollment ongoing

When administering agents with long $T_{1/2}$ in non-removable method
- May require an oral lead-in to assess toxicity before administering LA formulation.
- May have a prolonged sub-therapeutic tail which could lead to resistance should infection occur.
- More prolonged in women - issue of pregnancy

CAB LA Pharmacokinetic Tail After Drug Stopped
Men vs Women

Infection-Exposure-Resistance Relationships
Multiple Products with Multiple Delivery Systems in Preclinical to Clinical Trial Phase of Development

**ACTIVE DRUG**

- TAF
- TDF
- FTC
- NNRTI
- INSTI
- NRTI

**DELIVERY SYSTEM**

- Oral pills
- Vaginal gel
- Vaginal ring
- Vaginal film
- Suppositories
- Rectal gel
- Rectal suppositories
- Subcutaneous injection
- Inhalation
- Topical
- Vaginal barriers

**PRE-CLINICAL**

- Atritec
- CONRAD
- PATH
- Barbados
- Thailand
- South Africa
- Uganda
- United States
- World Health Organization
- University of Michigan
- University of Maryland
- University of California San Francisco
- University of Louisville
- University of Pittsburgh
- University of Washington
- University of California
- University of California Berkeley
- University of Chile
- University of Chile
- University of Hawaii
- University of Hong Kong
- University of Illinois
- University of Michigan
- University of Minnesota
- University of Minnesota
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Pennsylvania
- University of Penn
**PrEP: Broadly Neutralizing Antibodies**

Mgodi NM. IAS July 2019, Mexico City

**Safety and Efficacy of VRCo1 for Prevention of HIV Infection**

All get prevention package
Infusion q8 wk x 10, 22 mo FU

| VRCo1 10 mg/kg | N=900 | N=900 |
| VRCo1 30 mg/kg | N=900 | N=900 |
| Control       | N=900 | N=900 |

**HVTN 704/HPTN 085**
2700 MSM/TG Americas

**HVTN 703/HPTN 081**
1900 women sub-Saharan Africa

**Next Generation of bNAbss already under study:**
- Combinations
- Multi-specific

**BROADLY NEUTRALIZING ANTIBODY COMBINATIONS**

As with antiretroviral combinations used in treatment to control the virus, passive immunization of broadly neutralizing antibodies to protect against HIV will likely require two or more bNAbss that target different parts of the virus. There are many factors to consider when selecting bNAb combinations, including how many bNAbss and which ones work best together. Here we outline the bNAbss combinations being explored in early clinical studies.

**bNAb Cocktails: Two or more antibodies in a regimen**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Status</th>
<th>Research Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I</td>
<td>Planned</td>
<td>NIAID</td>
</tr>
<tr>
<td>Phase I</td>
<td>Suspended</td>
<td>NIAID</td>
</tr>
<tr>
<td>Phase I</td>
<td>Planned</td>
<td>CAPRISA, BIOMC, NIAID</td>
</tr>
<tr>
<td>Phase I</td>
<td>Planned</td>
<td>BiocMC, CALIVIR, NIAID</td>
</tr>
<tr>
<td>Phase I</td>
<td>Planned</td>
<td>Columbia University</td>
</tr>
</tbody>
</table>

**Combining bNAbss to broaden neutralization**

Different bNAbss have different neutralizing activities. Modeling and preclinical studies suggest the combining bNAbss may lead to broader neutralization compared to giving bNAbss alone, and multispecific antibodies might perform better than combinations. Clinical trials will validate whether these differences are seen in humans, and guide selection of best antibodies and combinations types.

*Data Mungel et al., 2015*

**Multispecific: Parts of two or more antibodies on a single antibody**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Status</th>
<th>Research Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I</td>
<td>Planned</td>
<td>Sanofi, NIAID</td>
</tr>
<tr>
<td>Phase I</td>
<td>Planned</td>
<td>Aurora Diamond AIDS Research Center (ADARC)</td>
</tr>
</tbody>
</table>
Topical and On-Demand PrEP Choices of the Future

Baeten J. IAS July 2019, Mexico City

- Dapivirine Vaginal Ring
- Open-Label Extension Studies
  - High uptake with good adherence
  - Well-tolerated
  - Lower HIV incidence than expected
  - 90-day ring in development
  - Planned submission FDA 2019
  - Evaluation across life-cycle: pregnancy/lactation (MTN 041, 042, 043), adolescents & post-menopausal women (MTN 023, 024, 034)

- Multi-Purpose Prevention Technology
- Tenofovir/levonorgesteral ring
- Dapivirine/levonorgesteral ring
- Pod rings containing ARV, contraceptives and anti-STI drugs

PrEP and Choice for Youth

MTN-034/REACH
n=300 AGYW aged 16-21
Kenya, South Africa, Uganda, Zimbabwe