Pregnancy, ARV Drugs, Viral Suppression, Pregnancy Outcome
Randomized Trial of RAL vs EFV-Based ART Started in Late Pregnancy: IMPAACT P1081

Mirochnick M et al.  CROI, 2019 Seattle Abs. 39LB

- Randomized trial of RAL+2NRTI vs EFV+2NRTI in 408 pregnant ART-naïve women S America, Africa, Thailand and US presenting to ANC at ≥28-36 weeks (later expanded to ≥ 20 weeks) gestation. Primary endpoint is virologic response (VL <200) at delivery.

<table>
<thead>
<tr>
<th>Delivery</th>
<th>Efavirenz</th>
<th>Raltegravir</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VL &lt;200</td>
<td>84% (151/179)</td>
<td>94% (174/183)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Enrolled 20 to &lt;28 wks</td>
<td>97% (87/90)</td>
<td>96% (85/88)</td>
<td>NS</td>
</tr>
<tr>
<td>Enrolled 28 to &lt;37 wks</td>
<td>71% (64/89)</td>
<td>93% (89/95)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Diagram:
- ART-naïve ≥20-36 wks gest
- 202 EFV + 2 NRTI
- 206 RAL + 2 NRTI
- Delivery
- 24 wk PP
More Rapid VL Decline with RAL than EFV
Mirochnick M et al. CROI, 2019 Seattle Abs. 39LB

- VL decline was greater in raltegravir arm than efavirenz arm at study weeks 2, 4 and 6.
- Both regimens well-tolerated; no difference AE, stillbirth, preterm.
- 1 raltegravir and 6 efavirenz infants were infected (p=0.06).

<table>
<thead>
<tr>
<th></th>
<th>Efavirenz</th>
<th>Raltegravir</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VL ↓ by wk 2 and sustained to delivery</td>
<td>84/131 (64%)</td>
<td>121/132 (92%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VL ≥2.0 log ↓decline or &lt;200 by wk 2</td>
<td>91/131 (69%)</td>
<td>123/132 (93%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VL &lt;1,000 all time pt after wk 4</td>
<td>117/123 (95%)</td>
<td>115/120 (96%)</td>
<td>NS</td>
</tr>
<tr>
<td>Stayed on study drug through delivery</td>
<td>129/131 (98%)</td>
<td>131/132 (99%)</td>
<td>NS</td>
</tr>
</tbody>
</table>
Open-label randomized trial of DTG+2NRTI vs EFV+2NRTI in 268 pregnant ART-naïve women presenting to antenatal clinic at ≥28-36 weeks gestation in Kampala and Cape Town.

Primary endpoint is virologic response (VL <50) at delivery.

Analysis at delivery (ITT): 122 DTG, 115 EFV

Median gestation age at enrollment, 31 weeks

No difference in baseline VL (median 4.4 log), CD4 (median 445), prior obstetric history, gestation, BMI
More Rapid VL Decline with Dolutegravir than Efavirenz
Khoo S et al. CROI 2019 Seattle, WA Abs 40LB

- **Primary outcome**
  - Time on medication before delivery, median 55 days

<table>
<thead>
<tr>
<th>Delivery</th>
<th>Dolutegravir</th>
<th>Efavirenz</th>
<th>aRR DTG vs EFV*</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VL &lt;50</td>
<td>73.8% (90/122)</td>
<td>42.6% (49/115)</td>
<td>1.66 (1.2, 2.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>VL &lt;1000</td>
<td>92.6% (113/122)</td>
<td>82.6% (95/115)</td>
<td>1.11 (1.0, 1.2)</td>
<td>0.0513</td>
</tr>
</tbody>
</table>

*Adjusted for age, country, VL (<> 100,000), CD4 (<>200), GA at start ART

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**Percent VL <50 c/mL**

- **Overall**
  - 73.7% (DTG), 78.9% (EFV)
  - Lower efficacy both at high RNA

**VL strata**

- VL <100,000: 42.6% (DTG), 48.9% (EFV)
- VL >=100,000: 44.4% (DTG), 14.3% (EFV)

**CD4 strata**

- CD4 >=200: 75.9% (DTG), 45.9% (EFV)
- CD4 <200: 57.1% (DTG), 23.5% (EFV)

**GA at entry strata**

- GA <36 wk: 74.5% (DTG), 44.1% (EFV)
- GA >=36 wk: 70.8% (DTG), 30.8% (EFV)
- Preterm rates similar (17% DTG, 16% EFV, similar to Botswana 18%)
- 4 stillbirths – all DTG arm
- 3 infant infections at birth (thought IU infection) – all DTG arm
ART Regimen and Viral Suppression in Pregnant Women, Brazil

Pascom ARP et al.  CROI 2019 Seattle, WA Abs. 760

- 8,539 pregnant women age >15 years (median 29 years); 38% ART naïve (63% RAL, 49% EFV), 42% ART >2 years.
- VL <50 c/mL 2-6 months after first prescription in pregnancy: overall 77%
  - Multivariate analysis, compared to EFV ART, 36% higher odds of suppression if on RAL (aOR 1.36, 1.1-1.7) and 49% lower odds suppression if using LPV/r (aOR 0.51, 0.4-0.7)

Other factors associated with suppression:
- Lower baseline VL
- Higher baseline CD4
- Older age
- Higher education level
- Lower time on ART
Nested case-control study (1 transmitting:3 non-transmitting mother-infant pairs) to evaluate maternal/infant drug resistance (DR) and MTCT:

- Cases: 85 transmitting mothers/infant:
  - 48 in utero/peripartum (IU)
  - 37 breastfeeding (BF)
- Control: 254 non-transmitting mothers matched by delivery date and site
Maternal ARV Resistance and MTCT, PROMISE
Boyce CL et al.  CROI 2019 Seattle, WA Abs. 769

- Maternal DR in transmitters at infant dx was associated with MTCT during BF but not IU/peripartum.
- After adjusting for HIV RNA, maternal DR was significantly associated with ↑ MTCT.

- DR in infant at diagnosis was higher in infants diagnosed BF vs IU/IP.
- Comparing DR at diagnosis, ART start and last visit, DR emerged over time (exposure of infant to maternal ART via BM or infant NVP prophylaxis or ART failure infant?).
- In those with DR, finding WT in mother and DR in infant at infant dx most common (suggesting DR arising de novo in infant).
Maternal HIV RNA After Delivery is Correlated with Infected Infant Pre-Treatment HIV RNA

Sakol-Mosethl M et al.  CROI 2019 Seattle, WA Abs.797

- Data from 40 mother-infant pairs from the Early Infant Treatment Study enrolled at <7 days from delivery (median 2 d).
- All infants received sdNVP at birth and AZT BID per MOH protocol until HIV dx, when changed to ART.
- Maternal RNA done at infant enrollment (median 2 d PP); infant RNA at baseline prior to ART.
- Higher maternal RNA correlated with higher pre-treatment infant RNA.
- Lowest infant RNA values in those exposed IU to DTG.

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No ART exposure (n=17) 42%</td>
<td>NA</td>
<td>64,072 [547,491512]</td>
<td>31,708 [&lt;40, &gt;10000000]</td>
<td>0.41 / 0.11</td>
</tr>
<tr>
<td>EFV-based ART (n=10) 25%</td>
<td>14 [1, 39]</td>
<td>10,259 [67, 144729]</td>
<td>1749 [1005, 1111950]</td>
<td>0.42 / 0.23</td>
</tr>
<tr>
<td>DTG-based ART (n=11) 27.5%</td>
<td>11 [1, 29]</td>
<td>56 [&lt;40, 85697]</td>
<td>310[79, 389270]</td>
<td>0.88 / &lt;0.001</td>
</tr>
<tr>
<td>LPV/r-based ART (n=2) 5%</td>
<td>NA*</td>
<td>29,085 [23912, 34257]</td>
<td>80,430 [17244, 143616]</td>
<td>NA*</td>
</tr>
<tr>
<td>Total (n=40)</td>
<td>2.5 [0, 40]</td>
<td>24,789 [&lt;40, 491512]</td>
<td>11,335 [&lt;40, &gt;10000000]</td>
<td>0.63 / &lt;0.001</td>
</tr>
</tbody>
</table>

* by Spearman’s correlation, * not applicable because of small sample size (n=2).
HBV Viremia and Adverse Infant Outcome in Women with HIV/HBV Coinfection

Bhattacharya D et al. CROI 2019 Seattle, WA Abs. 41

- Retrospective testing maternal samples from HPTN 046 (extended infant NVP for prevention postnatal transmission, 2007-2010) for HBV viral load at L/D.
- Of 2016 women, 88 (4.4%) had HBV/HIV coinfection; evaluated association of high HBV VL with infant outcomes.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HIV Alone (N=1953)</th>
<th>HIV/HBV (N=78) HBV &lt;10^6 IU/mL</th>
<th>HIV/HBV (N=10) HBV &gt;10^6 IU/mL</th>
<th>P value HBV &gt;10^6 vs HIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>LBW</td>
<td>194 (10%)</td>
<td>5 (6%)</td>
<td>3 (30%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Birth defect</td>
<td>83 (4%)</td>
<td>2 (3%)</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>HIV infection</td>
<td>71 (4%)</td>
<td>0</td>
<td>2 (20%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Infant death</td>
<td>75 (4%)</td>
<td>0</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>HIV/LBW</td>
<td>254 (13%)</td>
<td>5 (6%)</td>
<td>4 (40%)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

LBW: Covariates maternal age, CD4 at delivery, receipt of cART during pregnancy
Infection/death: Covariates maternal age, CD4 at delivery, receipt of cART during pregnancy, infant NVP assignment

- When compared to women with HIV alone, HIV/HBV coinfected women had association with infant LBW and HIV infection, adjusting for maternal CD4 and maternal cART.
- Reducing HBV VL may have benefit beyond prevention of HBV MTCT.
Adverse Birth Outcome in Women with HIV Acquired Perinatally vs Sexually, Botswana

Fennell C et al. CROI 2019 Seattle, WA Abs. 752

- Compared pregnancy outcome in 255 women with perinatal HIV vs 6,773 women with sexually-acquired HIV in birth surveillance study.
- Perinatal women younger (20 vs 24 years); more likely primagravida (77.6% vs 35.5%); & more likely receiving NVP-based ART in pregnancy.
- Only SGA more frequent with perinatal infection *unadjusted* analysis.
- Multivariate analysis, only NVP-ART associated with adverse outcome.

### Initial ART Regimen Prescribed or Continued During Pregnancy

<table>
<thead>
<tr>
<th>Initial ART Regimen</th>
<th>Percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NVP-Based ART</td>
<td>38.4%</td>
</tr>
<tr>
<td>EFV-Based ART</td>
<td>56.7%</td>
</tr>
<tr>
<td>Other &amp; Unknown</td>
<td>5.2%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Condition</th>
<th>RR (95%CI)</th>
<th>aRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm Delivery</td>
<td>1.09 (0.87, 1.37)</td>
<td>1.20 (0.93, 1.56)</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>0.76 (0.31, 1.83)</td>
<td>0.90 (0.34, 2.34)</td>
</tr>
<tr>
<td>Neonatal Death</td>
<td>0.48 (0.12, 1.91)</td>
<td>0.53 (0.12, 2.31)</td>
</tr>
<tr>
<td>Congenital Abnormalities</td>
<td>0.83 (0.37, 1.85)</td>
<td>0.91 (0.38, 2.15)</td>
</tr>
<tr>
<td>LBW²</td>
<td>1.16 (0.90, 1.49)</td>
<td>0.94 (0.71, 1.25)</td>
</tr>
<tr>
<td>SGA</td>
<td>1.33 (1.07, 1.65)</td>
<td>1.06 (0.83, 1.35)</td>
</tr>
</tbody>
</table>

1 Adjusted for initial ART regimen prescribed or continued during pregnancy, maternal age, gravidity, education, occupation, and income.

### Multivariate Analysis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Any Adverse Outcome¹,‡</th>
<th>Any Severe Adverse Outcome²,‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHIV (n=255)</td>
<td>1.13 (0.97, 1.32)</td>
<td>0.81 (0.67, 1.15)</td>
</tr>
<tr>
<td>Maternal Age</td>
<td>1.00 (0.99, 1.01)</td>
<td>1.01 (0.99, 1.05)</td>
</tr>
<tr>
<td>Gravida</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-5</td>
<td>0.95 (0.77, 1.18)</td>
<td>0.77 (0.49, 1.19)</td>
</tr>
<tr>
<td>2-4</td>
<td>0.87 (0.80, 0.94)</td>
<td>0.72 (0.61, 0.85)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tertiary/Secondary</td>
<td>0.93 (0.83, 1.05)</td>
<td>0.91 (0.71, 1.17)</td>
</tr>
<tr>
<td>Primary/None</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salaried</td>
<td>1.10 (0.93, 1.30)</td>
<td>0.85 (0.63, 1.16)</td>
</tr>
<tr>
<td>Non-Salaried</td>
<td>1.24 (1.08, 1.44)</td>
<td>1.08 (0.82, 1.43)</td>
</tr>
<tr>
<td>Student</td>
<td>Reference</td>
<td>Reference</td>
</tr>
</tbody>
</table>

³Other ART Regimen includes any LPV, EFV, or DTG-based ART

1. Any adverse outcomes include preterm delivery, small for gestational age, neonatal death, and stillbirth.
2. Any severe adverse outcomes include very preterm delivery (<32 weeks), very small for gestational age (<3rd%), neonatal death, and stillbirth.

³Adjusted for initial ART regimen prescribed or continued during pregnancy, maternal age, gravidity, occupation, education.
Timing Maternal ART and Stillbirth, Malawi
Msukwa MT et al. CROI 2019 Seattle, WA Abs. 754

- Evaluated rate stillbirth among women on ART who delivered singleton live birth or stillbirth at GA ≥28 wks between 2012 and 2015 at 20 clinics; overall rate stillbirth 2.5%. ART initiation stratified by:
  - ART before pregnancy: 5,961 (71%)
  - ART 1st/2nd trimester: 1,128 (14%)
  - ART 3rd trimester or labor: 1,291 (15%)

- Timing of ART initiation was not associated with stillbirth.

- Predictors of stillbirth: older maternal age (>35 years), delivery at <34 weeks gestation, breech vaginal delivery, and any maternal obstetric complication.
Dolutegravir and Other Integrase Strand Transfer Inhibitors (InSTI) in Pregnancy
DTG in Breast Milk - DolPHIN
Dickinson L et al.  CROI 2019 Seattle, WA Abs. 757

- RCT PK study of DTG vs EFV ART in late pregnancy (>28 weeks).
- Evaluated maternal plasma, cord blood and breast milk DTG levels, used for population PK modeling.

Median cord AUC\(_{0-24}\) was 41.2 mg.h/L - 123% that of maternal plasma at delivery

Average DTG milk concentration was 0.05 mg/L; median breast milk AUC\(_{0-24}\) was 1.2 ng.h/L, 3.3% maternal plasma at 1-3 d post switch to EFV; average daily infant dose estimated 2.2 ug/kg/day.

(note: switch to EFV 2wk PP, sampled at 1-3 days post switch)
4 hospital defect surveillance: 69,766 births (6,494 to HIV+ women, 80% on TDF-3TC-EFV (no DTG used in country yet)

<table>
<thead>
<tr>
<th>NTD</th>
<th>#</th>
<th>HIV-</th>
<th>HIV+</th>
<th>NTD% births HIV- women</th>
<th>NTD% births HIV+ women</th>
</tr>
</thead>
<tbody>
<tr>
<td>NTD</td>
<td>71</td>
<td>66</td>
<td>5</td>
<td>0.11% (0.08-0.13)</td>
<td>0.07% (0.03-0.17)</td>
</tr>
</tbody>
</table>

Tsepaomo NTD prevalence:
HIV- women: 0.09% (95% CI 0.07-0.12%)
HIV+ EFV preconception: 0.05% (95% CI 0.02-0.15%)

Phenotypes of the 71 NTD:
- Spina Bifida: 41 (58%)
- Anencephaly: 19
- Encephalocele: 12
French Perinatal Cohort: 808 infants InSTI exposure (87% RAL, 7% DTG):
  - G1: exposed conception (301); G2, G3: started pregnancy as 1st or 2nd line (intensification) (183, 324, respectively)

Within groups, matched 1:1 InSTI unexposed infant matched by other drugs, ethnicity, center, year delivery and GA at ART start

Rate birth defects and stillbirths trend to be ↑ in InSTI conception vs during pregnancy but not significant

No NTD with InSTI

In case-control InSTI (any time exposure) vs non-INSTI did not differ in birth defects, stillbirth or PTD.
Merck Review of Raltegravir-Exposed Pregnancies
Shamsuddin HH et al. CROI 2019, Seattle WA Abs. 745

- Merck review of database on 2426 pregnancies with RAL exposure, including data from:
  - Merck safety database, including APR
  - UK/Ireland National Surveillance HIV in Pregnancy and Childbirth (NSHPC)
  - French Perinatal Cohort (includes data from abstract 774)
- **Prospective:** 1991 cases, with 456 periconception RAL: no NTD
- **Retrospective:** 435 retrospective reports (no denominator), 4 NTD cases – 1 with periconception exposure; also 1 encephalocele with periconception exposure (APR)
- NSHPC (*Rasi V et al. JAIDS 2018 Nov 20 epub*) also reported on 33 EVG exposures → 26 preconception → no birth defects
Antiretroviral Pregnancy Registry (APR): Integrase Inhibitors (InSTI) and Neural Tube Defects (NTD)

Albano J et al.  CROI 2019 Seattle, WA Abs. 747

- Evaluation of the prevalence of NTD with InSTI exposure in prospective and retrospective components of the APR (through 31 Jul 2018).

APR Methods

- Prospective APR = primary analysis: Clinicians register pregnant women (no identifiers) with prenatal ARV exposures before pregnancy outcome is known, report data on exposure throughout pregnancy, and provide birth outcome data.

- Retrospective APR = secondary review: Reports of exposed pregnancies after pregnancy outcome is known; no denominator.

- Through 31 Jul 2018: includes 20,064 pregnancies with 20,413 fetal outcomes including 19,005 live births.

- APR reports come from North America (75%), Europe (8%), Africa (7%), South America (6%) and Asia (4%).

* MACDP = Metropolitan Atlanta Congenital Defects Program; TBDR = Texas Birth Defects Registry
Prospective Antiretroviral Pregnancy Registry (APR): Integrase Inhibitors (InSTI) and Neural Tube Defects (NTD)

Albano J et al. CROI 2019 Seattle, WA Abs. 747

- 1,193 live births with InSTI exposure at any time in pregnancy; 604 periconceptional exposure, including 174 DTG, 186 EVG, 244 RAL.
- 2 CNS defect cases were reported with InSTI exposure at any time (both DTG, one 1st trimester, one 2nd/3rd trimester).
- There were no NTD among prospective cases for any InSTI drug.

<table>
<thead>
<tr>
<th>Earliest Trimester of Exposure – Prospective Cases</th>
<th>Periconception</th>
<th>1st Trimester</th>
<th>2nd/3rd Trimester</th>
</tr>
</thead>
<tbody>
<tr>
<td>Defects/live birth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exposure to any INSTI</td>
<td>16/604 (2.6%)</td>
<td>4/135 (3.0%)</td>
<td>17/452 (3.8%)</td>
</tr>
<tr>
<td>Dolutegravir</td>
<td>6/174 (3.4%)</td>
<td>2/55 (3.6%)</td>
<td>4/137 (2.9%)</td>
</tr>
<tr>
<td>Elvitegravir</td>
<td>5/186 (2.7%)</td>
<td>0/27 (0%)</td>
<td>0/57 (0%)</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>5/244 (2.0%)</td>
<td>4/68 (5.9%)</td>
<td>13/290 (4.5%)</td>
</tr>
</tbody>
</table>

Can be more than one organ system for a defect

**No Neural Tube Defects**

CNS: 2: 1 (lissencephaly – neural migration disorder) with preconception DTG; 1 (ventriculomegaly) with 2nd/3rd trimester DTG exposure.

Face, ear, face, neck: 2
Cleft lip/palate: 2
Respiratory: 1
Cardiac/circulatory: 11
Lower GI: 1
Renal: 4
Musculoskeletal: 8
Chromosome abnl: 2
Other organ systems: 1
Specified syndromes 1
There were 7 NTD plus 2 encephalocele cases reported with InSTI exposure in retrospective reports to the APR (reported after delivery with defect that has occurred, no denominator, not included in prospective data review).

### Summary of Retrospective NTD and Encephalocele Cases with InSTI Drug Exposure through July 2018

<table>
<thead>
<tr>
<th>Dolutegravir [timing of exposure, country]</th>
<th>Raltegravir [timing of exposure, country]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iniencephaly [P, BW]</td>
<td>Myelomeningocele [T2, UK]</td>
</tr>
<tr>
<td>Encephalocele [P, BW]</td>
<td></td>
</tr>
</tbody>
</table>

P = periconception, T2 = second trimester, unk = unknown; BW = Botswana, PR = Puerto Rico, UK = United Kingdom, US = United States
Pharmacovigilance Databases and NTD

Hill A et al CROI 2019, Seattle, WA 2019 Abs. 747

- NTDs analysed for 4 INSTI (DTG, RAL, EVG, BIC), 2 PI (DRV, ATV), and 2 NNRTI (NVP, EFV) in 4 PV databases with data available online: FDA Adverse Event Reporting Systems (FAERS); WHO VigiAccess (WHO); European EudraVigilance (EU), UK Medicines Health Regulatory Authority (MHRA)

- Adverse drug reactions in the System Organ Class “Congenital or Familial Disorders” searched for potential NTDs (NTD, spina bifida, meningocele, meningomyelocele, anencephaly, iniencephaly, and encephalocele).

<table>
<thead>
<tr>
<th></th>
<th>FDA FAERS</th>
<th>EU EudraVigilance</th>
<th>WHO VigiAccess</th>
<th>UK MHRA</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTG</td>
<td>6</td>
<td>0</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>RAL</td>
<td>5</td>
<td>4</td>
<td>17</td>
<td>2</td>
</tr>
<tr>
<td>EVG</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>BIC</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>DRV</td>
<td>3</td>
<td>3</td>
<td>16</td>
<td>3</td>
</tr>
<tr>
<td>ATV</td>
<td>6</td>
<td>2</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>EFV</td>
<td>13</td>
<td>5</td>
<td>34</td>
<td>0</td>
</tr>
<tr>
<td>NVP</td>
<td>14</td>
<td>6</td>
<td>30</td>
<td>3</td>
</tr>
</tbody>
</table>

→ As would be expected, NTD seen with multiple ARVs, esp those with more frequent use in population.

→ Lack of agreement on #s between databases – and probable duplications
### Abs. 750 Masasa et al. Botswana
- Ultrasound fetal biometry in 435 pregnant women 16-36 weeks GA
  - 167 HIV-uninfected (mean 26 wk GA)
  - 268 HIV (mean 28 wk GA) (176 DTG 92 EFV ART)
- No significant differences between uninfected and HIV+ women on ART
- No significant differences HIV+ women on DTG and EFV ART

### Abs. 751 Kgole S et al. Botswana
- Birth anthropometry in 463 infants:
  - 275 HIV-exposed, 158 DTG/117 EFV
  - 188 HIV-unexposed
- No significant difference in WAZ or LAZ between HEU/HUU or DTG/EFV.
- Following clinical safety alert, clinic response plan developed; all women <55 years on DTG identified and contacted → group counseling session (15/grp)
- Women childbearing potential referred for pregnancy testing, evaluation of pregnancy intention in next 12 mos, and effective FP offered.
- Women intending to conceive offered EFV-ART; women could choose to remain on DTG without FP signing informed choice declaration.

9% (692/7963) were women on DTG, 95% (658) reviewed by 9/2018
510 women of reproductive potential (med age 37 yr, med duration DTG 4.3 mos)
5% (23/510) HCG+, all initial ultrasounds no deformities
Maternal Health Issues
Incident Infection in Pregnancy, Botswana
Mayondi GK et al. CROI 2019 Seattle, WA Abs. 733

- As part of Tsepamo birth surveillance study, HIV status abstracted from all women delivering 8 hospitals Botswana.
- Analyzed women not known to be infected at start of pregnancy for seroconversion.

- 39 seroconversions in 15,490 pregnant women with ≥2 tests = HIV incidence 6.5/1000 person years
- Median GA at seroconversion was 29 weeks; 90% started ART before delivery.
- Among 5,547 women without a 3rd trimester test, estimate 10 seroconversions may have been missed due to lack of testing

- As MTCT rates among women with known HIV infection decrease, the proportion of MTCT due to seroconversion during pregnancy will be increasingly important.
Cross-sectional study 242 pregnant women attending public ANC in Cape Town (106, 44% HIV+), testing for STI at 1\textsuperscript{st} ANC visit.

- Overall STI prevalence 33%: HIV+ 39%, HIV- 28\% (p=0.04)

Factors associated with STI, adjusting for GA and age: unmarried/not cohabiting; HIV infection; recent STI symptoms.
Potential Concern for Timing of DMPA Injection in Women Treated for HIV and TB

Mngqibisa R et al.  CROI 2019 Seattle, WA Abs. 78

- Study to evaluate whether concurrent use of EFV and RIF will decrease clearance of MPA resulting in potential reduced contraceptive efficacy.

- Estimate optimal dosing frequency for DMPA based on target serum MPA level of >0.1 ng/mL.

42 women with HIV/TB, not pregnant, stable on EFV ART >4 weeks, & on continuation phase of TB treatment (INH/RIF)

- MPA levels ≥0.1 ng/mL all through week 8.
- At week 10, 1 woman (2.4%) had level <0.1 ng/mL.
- At week 12, 5 women (11.9%) level <0.1 ng/mL.
- However, progesterone stayed low suggesting no ovulation.
- Consider shortening DMPA interval from 12→8-10 week with EFV/RIF coadmin?
PMTCT Cascade - Male Partner Testing

WHERE CAN I GET AN HIV TEST?
- Health clinics and hospitals
- Family planning or antenatal clinics
- Drug and alcohol services
- By mail order or online (in some countries)
- Specialist HIV/sexual health services and voluntary counselling and testing (VCT) sites
- Youth drop-in centres
- Community testing sites in workplaces, schools or religious facilities
Self-Tests for At-Home Partner Testing for Women in ANC, Kenya

Pintye J et al. CROI 2019 Seattle, WA Abs. 926

- Self-tests for at-home partner self-testing offered to 758 HIV-uninfected women seeking routine ANC at 10 facilities in Kenya.
- Instructed on use and received ≥2 or more oral-fluid tests.
- Data on outcomes assessed at 1 month in person FU visit.

63% of women with partner with unknown status accepted HIVST kits; of 390 with FU data, 76% had offered to partner; of 296 with partner data, 93% had tested.
Randomized Trial on Index HIV Self-Testing for Partners of ART Clients, Malawi

Dovel K et al.  CROI 2019 Seattle, WA  Abs.93

New ART clients >15 yrs with partner >15 yr, unknown HIV status, no hx IPV, lives in catchment area.

**Standard of Care (N=135):** Passive partner referral slip

- Index take slip home to partner; slip asks partner to attend nearest health facility; disclosure counseling

**Index HIVST (N=349):** Oraquick HIV ST

- Index given SOC and HIVST kit; demonstration of HIVST, local tailored HIVST instructions; counseling

**Randomized 1:2.5**

- 365 ART clients completed FU survey (75% retention)
  - 107 SOC
  - 258 HIVST
- 161 partners completed FU survey (62% response rate)

**Sites:** 3 district hospitals

**Data Collection:** March 2018-January 2019

- **ART Client:** Baseline and follow-up survey
- **Partner (Index HIVST only):** follow-up survey
- **Medical Chart Review:** 6-month follow-up

**Outcome Measures**

<table>
<thead>
<tr>
<th>Data Source</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>ART Client: 4-week follow-up survey</td>
<td>HIV testing, positivity rate, adverse events (self-report)</td>
</tr>
<tr>
<td>Partner (Index HIVST): 4-week follow-up survey</td>
<td>Usability (self-report)</td>
</tr>
<tr>
<td>Medical Chart Review</td>
<td>6-month ART initiation</td>
</tr>
</tbody>
</table>
Partner HIVST Acceptable and Increased Testing and Reached Men and Youth But ART Initiation Suboptimal

Dovel K et al.  CROI 2019 Seattle, WA  Abs.93

65% partners needed help and 8% couldn’t interpret

Similar partner distribution

More partners tested

Similar HIV+ prevalence

Partner return for ART start poor (23%)

Projected Use Services in Male Partners if 1000 Index Pts Received SOC vs HIVST

Test more men

Identify more HIV+ men

Linkage to care and ART start need to be improved
1,100 pregnant women seen at large health facility in South Africa with partner HIV- or unknown status offered 3 options for partner testing, Jan 2017-Oct 2017:

- Facility-based testing through invitation/workplace letters
- Home-based testing by trained counselor
- HIV self-testing taking up to 3 Ora-Quick self-test kids for themselves/partners

Incentives to encourage men to receive post-test counseling:

- Asked to send free “call me back” text to counselor after self-test → counselor returns call, collects test result and provides counseling; up to 25 rand (US $2) free airtime vouchers
- If HIV+, linked to treatment; if HIV-, linked to VMMC
Women: mean age 28 years, 72% single, 37% 1st pregnancy
- HIV prevalence 21% in women
- Facility: 223 men tested, 20 (9%) HIV+, 18 linked to care
- Home: 28 men tested, 2 (7%) HIV+, 1 linked to care
- Self test: 668 men tested - even with incentives, only 60% received post-test counseling, 23 (6%) self report HIV+, 14 got confirmatory testing, all linked to care

While HIV self-testing most popular, also most expensive per HIV dx; need operational research to improve linkage to confirmatory testing and care.
HIV- and ARV-Exposed Uninfected Children
SHINE: 2x2 factorial trial community cluster-based RCT compared effect of improved infant feeding, improved hygiene, or both vs SOC on outcomes, including growth and neurodevelopment.

Women were eligible if they lived permanently in trial clusters (catchment area of 1-4 village health workers) and were confirmed pregnant. Clusters randomized 1:1:1:1 to:

- **Control:** VHW encouraged early ANC, PMTCT uptake and EBF
- **IYCF:** VHW visited with interactive module for improved complementary feeding and 20gm nutri-butter per day between 6-18 mo/o
- **WASH:** ventilated improved pit latrine, handwashing stations, soap, chlorine, play space, hygiene counselling

Included 738 HIV-exposed and 3989 HIV-unexposed infants.
Zimbabwe SHINE Trial: HEU Children Have Worse Overall Mortality and Growth Outcomes Than HUU

Evans C et al.  CROI 2019 Seattle, WA Abs.790

- SHINE trial (2012-2015), children followed from birth with longitudinal HIV testing; compared outcomes 738 HEU & 3989 HUU to 18 mos.
- HIV-exposed children: 25/738 (3%) were known HIV-infected by 18 mos, 596 (81%) uninfected, and 117 (16%) unknown HIV status.
- Overall, HEU had worse outcomes than HUU children, with 39% higher 18-mo mortality and more growth abnormalities.
- Only 43% of HIV-exposed infants were alive, HIV-free and non-stunted at age 18 mos – despite half of children receiving nutritional intervention.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HEU (N=738)</th>
<th>HUU (N=3989)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-Month Mortality</td>
<td>7%</td>
<td>5%</td>
<td>0.04</td>
</tr>
<tr>
<td>Stunting</td>
<td>45.9%</td>
<td>30.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Underweight</td>
<td>17.4%</td>
<td>9.2%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Wasting</td>
<td>4.7%</td>
<td>2.5%</td>
<td>0.001</td>
</tr>
<tr>
<td>Microcephaly</td>
<td>9.5%</td>
<td>5.0%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Zimbabwe SHINE: HEU have Some Worse Early Childhood Development Outcomes Than HUU

Chandna J et al. CROI 2019 Seattle, WA Abs.784

- SHINE trial (2012-2015), children followed from birth with longitudinal HIV testing; compared early childhood development (ECD) measures in 205 HEU & 1175 HUU at age 24 mos.

- ECD outcomes at age 24 mos in HEU children differed from HUU in some (but not all) measures.

- HEU children had lower total developmental and motor and language scores; no difference in object permanence or self-control.

<table>
<thead>
<tr>
<th>24-month outcomes</th>
<th>HEU N=205</th>
<th>HIV-unexposed N=1175</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Difference between means</td>
<td>P</td>
</tr>
<tr>
<td>MDAT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td>90.6 (8.7)</td>
<td>92.4 (9.1)</td>
<td>-1.6 (-2.7, -0.5)</td>
</tr>
<tr>
<td>Gross motor</td>
<td>23.0 (2.9)</td>
<td>23.7 (3.1)</td>
<td>-0.6 (-0.9, -0.3)</td>
</tr>
<tr>
<td>Fine motor</td>
<td>22.8 (2.9)</td>
<td>22.3 (2.5)</td>
<td>-0.5 (-0.8, 0.0)</td>
</tr>
<tr>
<td>Language</td>
<td>20.5 (3.2)</td>
<td>21.4 (4.2)</td>
<td>-0.9 (-1.3, -0.2)</td>
</tr>
<tr>
<td>Social</td>
<td>34.3 (2.3)</td>
<td>34.2 (2.3)</td>
<td>0.1 (-0.2, 0.4)</td>
</tr>
<tr>
<td>MacArthur Bates CDI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vocabulary checklist</td>
<td>57.9 (19.2)</td>
<td>61.3 (18.8)</td>
<td>-3.2 (-6.0, -0.4)</td>
</tr>
</tbody>
</table>

Object permanence: 7.8 (1.4) 7.8 (1.4) 0.0 (-0.2, 0.2) 0.88

Self-control task:

<table>
<thead>
<tr>
<th></th>
<th>Percentage</th>
<th>Relative risk (95%CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hidden</td>
<td>64.5</td>
<td>64.1</td>
<td>1.01 (0.81, 1.21)</td>
</tr>
<tr>
<td>Unhidden</td>
<td>45.5</td>
<td>45.4</td>
<td>0.99 (0.89, 1.13)</td>
</tr>
</tbody>
</table>

MacArthur Bates CDI:

| Uses plurals   | 18.0    | 22.6    | 0.85 (0.65, 1.12) | 0.26 |
| Uses imperatives/progressives | 71.7    | 72.3    | 0.99 (0.91, 1.07) | 0.74 |
| Combines words | 97.6    | 98.7    | 0.99 (0.97, 1.01) | 0.27 |

Malawi Developmental Assessment Tool (MDAT): Gross and fine motor, language, and social components, adapted for rural Zimbabwean households

MacArthur Bates Communicative Development Inventory (CDI): Vocabulary and grammar checklist, translated and validated in Shona
ICYF but not WASH significantly decreased rate of stunting and anemia among HEU.

- HEU in ICYF group had ↓ stunting compared to non-ICYF groups (40% vs 50%, RR 0.81, 95% CI 0.68-0.97)
- HEU in ICYF group had ↓ prevalence anemia compared to non-ICYF (7% vs 14%, RR 0.52, 95% CI 0.34-0.79)
Evaluated the effect of the SHINE interventions on early childhood development of HEU children.

Early child development in HEU significantly improved with the combined infant feeding and sanitation intervention (but not individual).
ARV Drugs in Children
Dolutegravir in Children
CROI 2019 Seattle, WA

- **Frange P. Abs. 828 (France)**
  - 109 children (92% ART-exp, 11% prior InSTI) 5->18 yrs starting DTG
  - Pre-DTG suppression 58.7%; switch DTG ↑ to 79.8%, similar rates all ages
  - Low rate AE

- **Ruel T. Abs. 829LB (P1093)**
  - Age ≥6 mos-<2 yr and ≥2 yr-<6 yr PK study of higher dosing of dispersible tablet (DT)
  - Increased wt band DTG-DT dosing met pre-specified AUC24 and C24 targets both age groups.

- **Bollen P. Abs. 830LB (ODYSSEY)**
  - PK evaluation of 50 mg DTG tab and 30 mg DTG-DT in children 20-<25 kg (EMA rec dose 25 mg tab 20-<30kg).
  - Daily 50 mg DTG and 30 mg DT had similar PK profiles but Cmax (6.07-7.42 mg/L) was slightly higher than adults (5.41 mg/L).
Bunglawala FS. Abs.827

- Simulation of DTG dosing for neonates based on PK of RAL (metabolized UGT1A1) and midazolam (CYP3A4) in neonates.
- Different DTG dosing strategies simulated; target achieve levels ~ to those observed in pediatric ($C_{\text{trough}}$ 0.99 mg/L; $AUC_{24}$ 50.1 mg.h.L).

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Total Dose (mg)</th>
<th>Dose* (mg/kg)</th>
<th>$C_{\text{max}}$ (mg/L)</th>
<th>$AUC_{\text{av}}$ (mg.h/L)</th>
<th>$C_{\text{max}}$ (mg/L)</th>
<th>$AUC$ (mg.h/L)</th>
<th>$C_{\text{trough}}$ (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Too high</td>
<td>1</td>
<td>5 QD</td>
<td>1.4 (1.7 - 1.1)</td>
<td>3.99 ± 1.1</td>
<td>66.1 ± 22.9</td>
<td>2.3 ± 1.1</td>
<td>47.8 ± 14.3</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>4 QD</td>
<td>1.1 (1.3 - 0.9)</td>
<td>3.3 ± 0.6</td>
<td>47.0 ± 14.1</td>
<td>1.7 ± 0.6</td>
<td>35.1 ± 10.5</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>3 QD</td>
<td>0.85 (1 - 0.7)</td>
<td>2.4 ± 0.6</td>
<td>35.2 ± 13.4</td>
<td>1.3 ± 0.7</td>
<td>27.3 ± 9.2</td>
</tr>
<tr>
<td>Too low</td>
<td>4</td>
<td>2 QD</td>
<td>0.55 (0.7 - 0.4)</td>
<td>1.6 ± 0.3</td>
<td>23.5 ± 6.6</td>
<td>0.8 ± 0.3</td>
<td>18.0 ± 6.4</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>Day 1-7 = 2 QD, Day 8-28 = 3 QD</td>
<td>0.7 (1 - 0.4)</td>
<td>1.8 ± 0.7</td>
<td>30.5 ± 11.7</td>
<td>1.3 ± 0.7</td>
<td>25.9 ± 7.6</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>Day 1-7 = 2 QD, Day 8-28 = 3.5 QD</td>
<td>0.8 (1.2 - 0.4)</td>
<td>2.2 ± 1.4</td>
<td>35.4 ± 17.2</td>
<td>1.6 ± 1.1</td>
<td>28.8 ± 8.4</td>
</tr>
</tbody>
</table>

*Median(Range), neonate weight range in the model is 3.0 - 4.5kg. $C_{\text{max}}$: Maximum plasma concentration over 28 day simulations; $AUC_{\text{av}}$: Maximum plasma concentration after final dose has been administered; $AUC_{24}$: Average area under curve over 28 day simulations; $C_{\text{trough}}$: Minimum plasma concentration after final dose.

- Regimens 2, 3, 5 and 6 (>2 to 4 mg QD) result in PK parameters comparable to those in pediatric patients.

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Figure 1: PK profile showing average concentration of DTG ($C_{\text{avg}}$) from 0-28 days, (inset) DTG PK profile of daily doses.
Bictegravir/FTC/TAF Switch Study in Suppressed Pediatric and Adolescent Patients

Gaur A et al.  CROI 2019 Seattle, WA Abs.

- Wk 48 data from switch study: pt with RNA <50 x6 mos, CD4 ≥200
- PK study to confirm B/F/TAF dosing (50/200/25mg QD), followed by short-term safety study
- Favorable pill size

- AUC adolescents/children similar to adults
- $C_{trough}$ children ~same adults; ↓ in adolescents but still >11x > than $p_{aIC50}$
- FTC and TAF exposures similar adults

- Maintained viral suppression and CD4 count post switch
Early Treatment of Infants with HIV
- Non-randomized study in Botswana with early infant diagnosis and treatment.
- Screened 10,600 newborns, identified 44 HIV+ infants (0.4%) → 42 enrolled in EIT and start immediate ART (AZT/3TC/NVP then change at 2-5 weeks to AZT/3TC/LPV/r).
- 10 infants have complete testing at 84-96 weeks.

**Early ART**

**ANTEPARTUM group**
Test HIV+ within 96 hr after birth and start ART age <7 d
N=9

**PERIPARTUM group**
Test HIV- within 96 hr after birth and HIV+ within 5-42 d birth, start ART <57 d after birth
N=1

**Later ART**

**CONTROL group**
Enrolled 24-36 mo/o and started ART at age 30-365 d/o
N=10
Decline cell-associated provirus

Longitudinal Analysis EIT infants Only

Cross-Sectional Comparison: EIT, Control, Adults

→ ↓ intact & ↑ defective proviral DNA

EIT: early ART infants, 84/96 wk on ART
CONTROL: later ART infants, median wk 93 on ART
HAART: adults on ART, median 16 years ART
Compared VL decline in 25 infants started at <7 days vs 19 started at 7-28 days of life.

While overall probability of suppression at 48 weeks similar, the probability **early** suppression (by 3-6 mos) decreased by 35% for each week elapsed prior to starting ART.

**HR** = 0.65 (0.46, 0.92)
Observational study of 14 HIV+ infants starting ART age <6 wks
- Median age at diagnosis 4 d (0-17); median age ART start 8.5 d (0-36).
- Viral suppression 11/14 infants (78.6%) after median 143 d ART (13-469).
- Anemia 8 (53%) and neutropenia 5 (33%) but no interruption for toxicity.

Heterogeneity in baseline RNA levels
- Viral suppression 11/14 infants (78.6%) after median 143 d ART (range 13-469 d).
- One infant viral rebound >200 c/mL at 295 d; 10 remained suppressed throughout FU.
- One very early and prolonged suppression (66 to 958 d life).
VRC01-LS is broadly neutralizing anti-CD4 binding site monoclonal antibody with modified affinity for neonatal Fc receptor to increase T½.

Evaluated PK and safety of single (N=10) and multiple (N=11) subcutaneous dose VRC01-LS in HIV-exposed neonates (all receive ARV prophylaxis).

- Well tolerated (no Grade 3/4 AE).
- Can be administered at birth and 1-2 time per year to achieve desired levels – additional strategy to prevent postnatal MTCT?

- T½ : 59±8 days
- Week 12: mean 44.7 mcg/mL (33% >50, 100% >20 mcg/mL)
- Note: IC50 for most clade B, C and A isolates <10 mcg/mL; in NHP models, levels 20 mcg/mL well exceed protective level
Adolescents and HIV
Recent HIV Infection Adolescent Girls and Young Women, Malawi

Payne D et al.  CROI 2019 Seattle, WA Abs. 831

- Nov 2017-July 2018 enrolled pregnant women age 15-24 years newly dx with HIV at 1\textsuperscript{st} ANC visit at 121 facilities; recent infection testing algorithm (RITA) used to define recent infection.
- Among 54,643 attending 1\textsuperscript{st} ANC, HIV prevalence 4.3%; 1,159 had new HIV dx and eligible for study, 589 (50.9%) enrolled in study.

- 11.7% with new dx had recent infection $\rightarrow$ annualized incidence of 0.59%.
- Incidence higher among those aged 20-24 years (vs 15-19 years); Blantyre residence

Estimated of HIV incidence in pregnant adolescent girls and young women Malawi 2017-2018

- Prevalence recent infection
  - primary or less (n=372)
  - secondary or more (n=212)
  - never married (n=114)
  - currently married (n=433)
  - divorced, separated, widowed (n=25)
  - 1 (n=259)
  - 2 or more (n=288)
  - 1 (n=136)
  - 2-3 (n=324)
  - 4 or more (n=52)
  - similar age
  - 5-10 years older (n=146)
  - >10 years older (n=183)
  - Don't know (n=66)
  - negative (n=144)
  - positive (n=61)
  - unknown (n=352)
  - never (n=179)
  - < 12 months ago (n=194)
  - >=12 months ago (n=212)
Youth Psychiatric Trajectories in Perinatal HIV Infection or Exposure Predict Young Adult Viremia

*Nguyen N et al.  CROI 2019 Seattle, WA Abs. 819*

- Child and Adolescent Self-Awareness and Health (CASAH) longitudinal cohort of 340 youth with perinatal HIV exposure (206 PHIV, 134 PHEU) recruited from 4 centers in NYC at age 9-16 yrs; interview q 12-18 mos.
- Analysis focuses on baseline through FU#5 (ages 18-28 yrs); 3 psychiatric trajectories described:

**Consistent Low Psychiatric Disorder**
- N=231, 68%
- Baseline: No mood/behavioral disorder during FU
- Low and ↓ probability of anxiety disorders (from 19% to 0% FU5)
- ↑ but low probability substance use disorders (from 0% to 25%)

**Persistent anxiety**
- N=75, 22%
- Baseline: Persistent high probability of anxiety disorders during FU (~50%)
- Low and ↓ probability behavioral disorders (from 11% to 4%)
- Low but ↑ probability mood/substance use disorders (from 5-21% and 0-15%)

**Escalating Psychiatric Co-Morbidity**
- N=34, 10%
- Baseline: Substantial probability of comorbidity at enrollment (14% mood, 36% behavioral, 22% substance use, 39% anxiety)
- ↑ probability substance use (83%), anxiety (48%) and mood disorders (21%)

Baseline sociodemographic predictors of trajectory type and association with viremic event in last 12 mos of FU#5 (62% had at least 1 viremic event [VL >200 c/mL])

~1/3 of PHIV and PHEU had high burden psychiatric disorder, and nearly 2/3 had a viremic event in young adulthood.
PrEP in Adolescents and Women
LESSONS LEARNED

Similar findings across all projects:

- PreP interest and uptake is high (>90%) (HPTN 082).
- Risk score high
- STI prevalence ~30%
- IPV in past year 30-50%
- Depressive symptoms 42%
- Limited experience contraceptive pill taking.
Engaging Young Women in Sub-Saharan Africa: Lessons Learned
Delany-Moretiew S.  CROI 2019 Seattle, WA Abs.163

- PrEP should be offered as part of comprehensive youth-friendly services
  - Flexible hours, non-judgmental, provide for information needs
- Delivered as a part of a package of sexual and reproductive health services
  - Enhance engagement in care
  - Provide ongoing choice in context of changing risk
  - Refills for PrEP and contraception, Opportunity to add STI testing
  - Platform to introduce new products
- Respond to greatest health needs
  - Screening for violence as part of HCT
  - Referral for mental health services
  - Program benefits, efficiency, cost
Women 15-45 years seeking routine ANC, PNC and FP in 16 high volume facilities in Kenya screened for HIV risk and willingness to initiate PrEP; 2304 women initiated on PrEP.

Median age 24; 58% had partner unknown HIV status, 96% reported recent condomless sex.

Continuation at 1, 3 and 6 months was 38%, 21% and 10% overall; similar by delivery point.

Continuation of PrEP use at 3 months was independently higher among women with HIV positive male partners (p<0.01) and older women 35 years and above (p=0.02) (Figure 3); only partner HIV status independently associated with continuation at month 6.

Commonly reported reasons for stopping PrEP included low perceived risk of HIV (23%), experiencing side effects (19%), pill burden (17%), and that partner is HIV negative (17%).
High Adherence in Young Women Cape Town in First 3 Months After PrEP start

Celum CL et al. CROI 2019 Seattle, WA Abs.994

- 3 Ps for Prevention Study (Perception, Partners, Pills) enrolled 200 sexually active women 16-25 years; median age 19 years.
- Adherence at 3 months was assessed by tenofovir-diphosphosphate (TFV-DP) in dried blood spots. High adherence; TFV-DP >700 fmol/punch (>4 doses/week); Medium adherence 350-700 fmol/punch (2-3 doses/week).
- Retention 89% at 3 mos.
- Median TDF-DP was 622 at 1 mo, 707 at 2 mo; 700 at 3 mo.
  - At 3 months, 50% had high adherence and 80% had medium or greater adherence at 2 and 3 months.
- High adherence associated with: partner unknown or HIV+, disclosure of PrEP use.
451 sexually active HIV-negative women ages 16-25 were enrolled; 427 accepted PrEP (412 at enrollment, 15 after enrollment); median age 21 years (6% <18 years).

Adherence at 3 months was assessed by tenofovir-diphosphate (TFV-DP) in dried blood spots. High adherence; TFV-DP >700 fmol/punch (>4 doses/week); Medium adherence 350-700 fmol/punch (2-3 doses/week).

- 310/374 (84%) had TFV/DP detectable at mo 3
- Median TDF-DP was 485 fmol
  - 25% were 700 (high)
  - 23% 350-699 (medium)
  - 36% detectable <349
  - 16% undetectable

Predictors high vs low adherence: attend adherence support group, no depression, # sex partners
Pooled analysis comparative data on efficacy and safety of TAF vs TDF in women (stratified by ART naïve vs virally suppressed).

- Viral response (96 wks) same with TAF but bone and renal toxicity improved compared to TDF.
F/TAF Non-Inferior to F/TDF for PrEP: Discover Study

Hare CB et al.  CROI 2019 Seattle, WA Abs. 104LB

5387 high-risk MSM or TGW

94 sites, 11 countries: NA, EU

F/TAF 200/25 mg QD
N=2694

F/TDF 200/300 mg QD
N=2693

Double-blind Active control

96 Weeks

Primary analysis: HIV incidence/100 PY after 100% complete wk 48 and 50% complete wk 96

Non-inferiority margin upper 95% CI <1.62
Expected incidence 1.44/100 PY (IPrEx; PROUD; IPERGAY)

F/TAF non-inferior to F/TDF for prevention HIV infection in MSM/TGQ
Both well tolerated, low d/c
F/TAF had better bone and renal outcomes
TB and HIV

- Pregnancy
- Pediatrics
- General
Prospective cohort pregnant HIV+ women with and without TB disease in Soweto, S Africa, January 2011-July 2014, FU pregnancy to 12 mo PP for MTCT, pregnancy outcomes, maternal/infant mortality and TB.

Evaluated outcomes by IPT use (non-randomized, self-reported).

INH Prophylaxis for Latent TB, Pregnancy Tshepiso Cohort, South Africa
Salazar-Austin N et al. CROI 2019, Seattle, WA Abs. 77
IPT use in 2\textsuperscript{nd}/3\textsuperscript{rd} trimester during pregnancy was \textit{not} associated with a higher rate of poor maternal or infant outcomes in this cohort of 152 women, after controlling for CD4, VL, ART, maternal age, BMI and anemia.

---

**INH Prophylaxis for Latent TB, Pregnancy Tshepiso Cohort, South Africa**

Salazar-Austin N et al. CROI 2019, Seattle, WA Abs. 77

- **Adverse Pregnancy Outcome by IPT Use**

  - **TB disease:**
    - Maternal: 1 case (no IPT)
    - Infant: No cases

  - **Logistic Regression for having an adverse pregnancy outcome**

    |                | Unadjusted OR | 95% CI    | Adjusted OR | 95% CI    |
    |----------------|---------------|-----------|-------------|-----------|
    | **IPT**       |               |           |             |           |
    | Yes           | 2.02          | 0.92-4.67 | 2.79        | 1.13-7.39 |
    | No            |               |           |             |           |
    | **Maternal Age** |         |           |             |           |
    | <35 years     | 0.40          | 0.06-1.50 | 0.62        | 0.09-2.73 |
    | ≥35 years     |               |           |             |           |
    | **CD4**       |               |           |             |           |
    | ≥350 cells/mm\(^3\) |            | 0.14-0.85 | 0.24        | 0.08-0.64 |
    | <350 cells/mm\(^3\) |            |           |             |           |
    | **Viral Load** |               |           |             |           |
    | <1000 copies/μL |            | 0.54-3.22 | 2.16        | 0.65-7.21 |
    | ≥1000 copies/μL |            | 1.40-9.39 | 2.24        | 0.98-7.37 |
    | **PMTCT Regimen** |      |           |             |           |
    | CART          |               |           |             |           |
    | AZT monotherapy +/-sd NVP or no ART |        | 0.44-8.43 | 0.72        | 0.22-2.20 |
    | **BMI**       |               |           |             |           |
    | BMI ≥ 21.5 kg/m\(^2\) |            | 3.80-21.45 | 3.81        | 0.62-23.83 |
    | BMI < 21.5 kg/m\(^2\) |            |           |             |           |
    | **Anemia**    |               |           |             |           |
    | Hgb ≥ 10.5 g/dL |            | 7.13-156.11 | 16.30 | 1.24-421.67 |
    | Hgb < 8.5 g/dL |            |           |             |           |

*Adjusted for CD4, VL, ART type, maternal age, anemia

→ Higher risk adverse pregnancy outcome: no IPT, low CD4, anemia
**Tshepiso Cohort vs APPRISE RCT Trial**

**Tshepiso:** Observational 2nd/3rd trimester IPT (self-reported); 152 deliveries (69 IPT, 82 no IPT)

**APPRISE RCT:** RCT of immediate (2nd/3rd trimester) IPT vs deferred (12 wk postpartum) IPT; 962 deliveries (460 Immediate, 466 Deferred)

---

**TB disease:**
Maternal: 1 case (no IPT)
Infant: No cases

**Death:**
Maternal: 0 (IPT), 1 (no IPT)
Infant: 1 (IPT), 0 (no IPT)

---

**Tshepiso Adverse Pregnancy Outcome by IPT Use**

<table>
<thead>
<tr>
<th>Event</th>
<th>IPT (N=69)</th>
<th>No IPT (N=82)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal Demise</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Prematurity</td>
<td>10%</td>
<td>9%</td>
</tr>
<tr>
<td>LBW</td>
<td>22%</td>
<td>15%</td>
</tr>
<tr>
<td>Birth defect</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Composite</td>
<td>27%</td>
<td>22%</td>
</tr>
</tbody>
</table>

**No. events:** 1 1 7 18 6 10 1 2 11 23

- **p=1.00**
- **p=0.06**
- **p=0.60**
- **p=1.00**
- **p=0.09**

**APPRISE RCT Adverse Pregnancy Outcome by Immediate vs Deferred IPT**

<table>
<thead>
<tr>
<th>Event</th>
<th>Immediate IPT (N=460)</th>
<th>Deferred PP IPT (N=466)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal death</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>Prematurity</td>
<td>11%</td>
<td>9%</td>
</tr>
<tr>
<td>LBW</td>
<td>14%</td>
<td>10%</td>
</tr>
<tr>
<td>Birth defect</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Composite</td>
<td>23%</td>
<td>17%</td>
</tr>
</tbody>
</table>

**No. events:** 17 9 48 40 62 46 10 6 106 78

- **p=0.09**
- **p=0.29**
- **p=0.07**
- **p=0.26**
- **p=0.01**

---

**TB disease:**
Maternal: 3 (immediate), 3 (deferred)
Infant: 0 (immediate), 1 (deferred)

**Death:**
Maternal: 2 (immediate), 4 (deferred)
Infant: 11 (immediate), 17 (deferred)

---

**Severe pregnancy outcome composite:**
Immediate: 6.3%
Deferred: 4.6%
P=0.27
Improving Child TB Contact Management, Lesotho – PREVENT Study

Hirsch-Moverman Y et al. CROI 2019 Seattle, WA Abs.79

- Cluster-randomized trial of community-based intervention (10 clinics) vs SOC (10 clinics) to improve identification and screening of child contacts.
- All adult TB pt newly registered at clinics Jan 2017-June 2018 and child contacts included, with data collection from medical records.

**Target of CBI intervention**

<table>
<thead>
<tr>
<th>Step 1: Identification</th>
<th>Step 2: TB Screening</th>
<th>Step 3: PT Initiation</th>
<th>Step 4: PT Completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child contacts exposed to TB in the household are identified</td>
<td>All child contacts undergo screening per country guidelines</td>
<td>Child contacts who do not have TB disease considered eligible for preventive therapy</td>
<td></td>
</tr>
</tbody>
</table>

**Comparison of Study Interventions**

<table>
<thead>
<tr>
<th></th>
<th>SOC</th>
<th>CBI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Three I’s training</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Child contact screening for TB</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>PT provision to child contacts</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Child screening and PT provision training according to clinical algorithm</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Nurse mentorship and monitoring</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Health education in facilities and community for caregivers using PT literacy curriculum</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Community-based village health workers (VHW) working with facility-based VHW to link to services</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Consistent community support via VHW</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

**Identification:** # child contacts/adult case was low, not significantly different

**Screening:** More child contacts/adult case screened with CBI but not statistically significant

**Yield:** Non-significant trend for higher yield at CBI sites

- Adult TB cases in register 973 (64% male, 68% HIV+)
  - CBI (N=490): TB card located, contact filled out 484 (99%)
  - SOC (N=483): TB card located, contact filled out 314 (65%)
- Child contact ID per TB case
  - CBI (N=490): 216 (44%), 4/10 cases
  - SOC (N=483): 163 (34%), 3/10 cases
- Child contact ID and screened per TB case
  - CBI (N=490): 204 (94%), 4/10 cases
  - SOC (N=483): 101 (62%), 2/10 cases

\[p=0.08\]
Nevirapine PK is Modified by TB Therapy with Rifampin in Young Children
Kwara A et al. CROI 2019 Seattle, WA Abs.825

- HIV+ children with (N=30) or without TB (N=23) aged 3-35 months or <10kg started on NVP 200 mg/m² + 2NRTI with 2-week lead in.
- Proportion of children with NVP C_{min} <3 mg/L was 61% in HIV/TB coinfected children and 31% in HIV only (p=0.03).
- In multivariate analysis, TB coinfection and CYP2B6 516 genotype influenced NVP PK (differences only significant for CYP2B6 516GG and not GT or TT genotypes).

In 14 HIV/TB children with PK on and off RIF, NVP AUC_{0-12h} was ↓ by 34% & CL/F ↑ by 45% during coadministration of NVP/RIF.
Safety of Weekly INH/Rifapentine (3HP) in HIV+ Adults on DTG-ART

Dooley KE et al. CROI 2019, Seattle, WA Abs. 80LB

- 61 adults with suppressed VL on EFV-ART with indication for prophylaxis latent TB → switched to DTG (50 mg QD) ART x 8 wks (EFV washout) and then PK safety evaluated with weekly HP x 12 wks.

<table>
<thead>
<tr>
<th>AE</th>
<th>N</th>
<th>Prior to 1st HP dose</th>
<th>After 1st HP dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 2</td>
<td>2</td>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Grade 3</td>
<td>3</td>
<td>1&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>a</sup>GI disturbance; <sup>b</sup>flu-like reaction; <sup>c</sup>elevated creatinine <sup>d</sup>elevated creatinine, hypertension

- Trough DTG levels ↓ ~50% and AUC ↓ ~30% with HP, but median values >300 ng/mL all time points (IC90 64 ng/mL); viral suppression maintained (1 post-HP-treatment rebound 2300, with suppression on 2<sup>nd</sup> VL). **Concluded no dose increase needed.**
Test and Treat, Viral Load Testing, Viral Suppression
Impact of Universal Testing and Treatment in Zambia and South Africa – HPTN 071
Hayes RJ et al. CROI 2019, Seattle, WA Abs. 92LB

- Universal test and treat – 21 communities randomized to one of 3 arms (7 communities per arm); primary outcome HIV incidence.

### Pop-ART Combination Intervention

- **Arm A**
  - Full PopART intervention including immediate ART irrespective of CD4 count
- **Arm B**
  - PopART intervention except
  - ART initiation according to current national guidelines
- **Arm C**
  - Standard of care at current service provision levels including
  - ART initiation according to current national guidelines

2,500 random sample from each community (aged 18-44)
Population Cohort (N=52,500)
Followed up annually for 36 months

### Viral Suppression by Arm

<table>
<thead>
<tr>
<th></th>
<th>Pop-ART Immediate</th>
<th>Pop-ART National guide</th>
<th>SOC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral suppression</td>
<td>1531/2159 (72%)</td>
<td>1318/1891 (68%)</td>
<td>1480/2183 (60%)</td>
</tr>
<tr>
<td>Adjusted prevalence ratio*</td>
<td>1.16 (0.99, 1.36)</td>
<td>1.08 (0.92, 1.27)</td>
<td>1</td>
</tr>
<tr>
<td>VS compared to SOC</td>
<td>16% increase</td>
<td>8% increase</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.07</td>
<td>0.30</td>
<td></td>
</tr>
</tbody>
</table>

Adjusted for age category, sex
Impact of Universal Testing and Treatment in Zambia and South Africa – HPTN 071
Hayes RJ et al. CROI 2019, Seattle, WA Abs. 92LB

Primary endpoint: Incidence PC12 to PC36 by Community

- PopART achieved first 2 UNAIDS 90-90 targets
- PopART with ART by local guidelines reduced incidence by 30% in these high burden settings
- Community-based services for universal HIV testing and linkage are key component of global combination prevention

Primary endpoint: Incidence in PC12-PC36

<table>
<thead>
<tr>
<th></th>
<th>Pop-ART Immediate</th>
<th>Pop-ART National guide</th>
<th>SOC</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV incidence</td>
<td>198/12,990 (1.45%)</td>
<td>157/14,149 (1.06%)</td>
<td>198/12,563 (1.55%)</td>
</tr>
<tr>
<td>Adjusted rate ratio*</td>
<td>0.93 (0.74, 1.18)</td>
<td>0.70 (0.55, 0.88)</td>
<td>1</td>
</tr>
<tr>
<td>Incidence compared to SOC</td>
<td>7% reduction</td>
<td>30% reduction</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.51</td>
<td>0.006</td>
<td></td>
</tr>
</tbody>
</table>

* Adjusted for age category, sex and baseline community HIV prevalence; reported numbers include imputation for PC12 and PC24 missed visits
Pair-matched communities randomized trial 30 communities Botswana, October 2013, interventions ended March 2018, FU completed April 2018

**Intervention (15 communities)**
- Community mobilization
- Home-based and mobile HIV testing campaigns, targeted testing
- Linkage to care support: scheduled clinic visits, SMS reminder, active tracing if missed apt
- Early ART (universal from June 2016 at 1st visit)
- Strengthened VMMC

**SOC (15 communities)**
- ART if CD4 <350 or WHO III/IV or pregnant until June 2016 when moved to universal ART

Intervention uptake assessed through end-of-study survey in communities not in longitudinal cohort

Selected 1 pair of communities per region
HIV Diagnosis, ART, Suppression and VMMC Increased in Both Arms, with Greater Increase in Intervention

Wirth K et al. CROI 2019 Seattle, WA Abs.95

- Significant increase across cascade with intervention.

542,138 pts, 65% female; median age 34.5 years, median FU 44.9 months; 51% started ART 2009-2013, 30% 2014-2018

Scale up VL testing in some but not all countries: 3 countries have scaled up VL testing (black): Malawi, S Africa, Zimbabwe.

CD4 count at ART start has ↓ (advanced disease may go undetected); VL testing low levels; advanced disease ↓ in 2017 ~20%; failure ~10% without much change.
Factors Associated with Persistent Viremia with Universal Test and Treat, Uganda

Patel EU et al. CROI 2019 Seattle, WA Abs.96

- Rakai Community Cohort Study of adults 15-49 years, 5 surveys Nov 2011 and Feb 2017
- HIV VL measured in all HIV+ persons in 2011, 2015 and 2016

Factors associated with persistent viremia included:
- Being young (<29 years)
- Being Male
- Never Marries
- Recent in-migration

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Crude RRR (95% CI)</th>
<th>Adjusted RRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age group, years</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15-29</td>
<td>1.91 (1.28-2.83)</td>
<td>1.83 (1.22-2.75)</td>
</tr>
<tr>
<td>30-39</td>
<td>1.46 (0.99-2.16)</td>
<td>1.55 (1.05-2.29)</td>
</tr>
<tr>
<td>40-49</td>
<td>Ref.</td>
<td>Ref.</td>
</tr>
<tr>
<td><strong>Male sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>Ref.</td>
<td>Ref.</td>
</tr>
<tr>
<td>Previously married</td>
<td>0.82 (0.64-1.05)</td>
<td>0.92 (0.72-1.18)</td>
</tr>
<tr>
<td>Never married</td>
<td>2.38 (1.71-3.31)</td>
<td>1.82 (1.30-2.55)</td>
</tr>
<tr>
<td><strong>Marital status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>Ref.</td>
<td>Ref.</td>
</tr>
<tr>
<td>Primary</td>
<td>1.07 (0.75-1.54)</td>
<td>1.00 (0.70-1.43)</td>
</tr>
<tr>
<td>Secondary or more</td>
<td>1.38 (0.87-2.18)</td>
<td>1.43 (0.92-2.24)</td>
</tr>
<tr>
<td><strong>Educational attainment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>Ref.</td>
<td>Ref.</td>
</tr>
<tr>
<td>Primary</td>
<td>Ref.</td>
<td>Ref.</td>
</tr>
<tr>
<td>Secondary or more</td>
<td>1.38 (0.87-2.18)</td>
<td>1.43 (0.92-2.24)</td>
</tr>
<tr>
<td><strong>Migration status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Permanent resident</td>
<td>Ref.</td>
<td>Ref.</td>
</tr>
<tr>
<td>In-migrant (0-2 years)</td>
<td>1.37 (0.98-1.91)</td>
<td>1.95 (1.36-2.80)</td>
</tr>
<tr>
<td>In-migrant (&gt;2 years)</td>
<td>1.12 (0.75-1.68)</td>
<td>1.45 (0.97-2.17)</td>
</tr>
<tr>
<td><strong>Alcohol use (past year)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of sex partners (past year)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>Ref.</td>
<td>Ref.</td>
</tr>
<tr>
<td>2-3</td>
<td>1.33 (1.05-1.70)</td>
<td>0.94 (0.73-1.20)</td>
</tr>
<tr>
<td>&gt;3</td>
<td>1.96 (1.46-2.65)</td>
<td>1.20 (0.88-1.64)</td>
</tr>
</tbody>
</table>

* Adjusted for index survey visit, age, sex, marital status, education status, migration status, alcohol use, and number of sexual partners.
RCT at public clinic in Durban S Africa in adults >18 years presenting for 6 month post ART start FU visit

- Intervention: POC viral load testing (Xpert) and same day counseling with task shifting to nurse for stable pt
- SOC: lab viral load testing and care from nurse)

Primary outcome: 12 mo viral suppression and retention (pick up drugs)

<table>
<thead>
<tr>
<th></th>
<th>Intervention Arm</th>
<th>Standard-of-care Arm</th>
<th>Absolute Risk Difference</th>
<th>Non-inferiority (1-side 95% CI)</th>
<th>Superiority (2-side 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral suppression (&lt;200 copies/mL) and Retention in care at study clinic</td>
<td>89.7% (175/195)</td>
<td>75.9% (148/195)</td>
<td>13.9%</td>
<td>(≥7.6)</td>
<td>(6.4-21.2)</td>
</tr>
</tbody>
</table>

After 12 mo clinical FU, the intervention increased viral suppression and retention in care at the study clinic by 13.9% (95% CI 6.4-21.2%).

Total pt visit duration for POC VL testing was 2½ - 3 hours
## Secondary outcomes

### Viral suppression <50 c/mL and retention

<table>
<thead>
<tr>
<th></th>
<th>Intervention Arm (N=195)</th>
<th>Standard-of-Care Arm (N=195)</th>
<th>Absolute Risk Difference</th>
<th>Superiority P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral suppression (&lt;200 copies/ml)</td>
<td>93.3%</td>
<td>83.1%</td>
<td>10.3%</td>
<td>0.003</td>
</tr>
<tr>
<td>Retention in care at study clinic</td>
<td>92.3%</td>
<td>84.6%</td>
<td>7.7%</td>
<td>0.026</td>
</tr>
<tr>
<td>Viral suppression ≤50 copies/mL and retention in care</td>
<td>85.6%</td>
<td>71.3%</td>
<td>14.4%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Viral suppression &lt;200 copies/ml and retention in care at any clinic</td>
<td>90.8%</td>
<td>78.5%</td>
<td>12.3%</td>
<td>0.001</td>
</tr>
</tbody>
</table>

### Entry VL and Communication of Results

<table>
<thead>
<tr>
<th>Entry of viral load result into health information system</th>
<th>Intervention Arm</th>
<th>Standard-of-Care Arm</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median [IQR] days to enter viral load result in health information system</td>
<td>100%</td>
<td>100%</td>
<td>0%</td>
</tr>
<tr>
<td>Communication of viral load result to patient</td>
<td>99.8%</td>
<td>81.5%</td>
<td>18.3%</td>
</tr>
<tr>
<td>Median [IQR] days to communicate viral load result to patient</td>
<td>0 [0-0]</td>
<td>28 [28-54]</td>
<td>28 days</td>
</tr>
</tbody>
</table>

### Follow-Up HIV Care and Treatment

<table>
<thead>
<tr>
<th>Switch to second-line ART after viral failure (&gt;1,000 copies/ml x2)</th>
<th>Intervention Arm</th>
<th>Standard-of-Care Arm</th>
<th>Cox Hazard Ratio</th>
<th>Superiority P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>6/6 (100%)</td>
<td>4/9 (44%)</td>
<td>--</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Median [IQR] days to switch to second-line ART after viral failure</td>
<td>1 [0-7]</td>
<td>76 [29-134]</td>
<td>10.9</td>
<td>0.005</td>
</tr>
<tr>
<td>Referral into community-based ART delivery program</td>
<td>116 (60%)</td>
<td>52 (27%)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Median [IQR] days to referral into community-based ART program</td>
<td>168 [168-175]</td>
<td>261 [231-281]</td>
<td>3.5</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### Healthcare Utilization

<table>
<thead>
<tr>
<th>Total clinic visits per patient</th>
<th>Intervention Arm</th>
<th>Standard-of-Care Arm</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.2 ±1.6</td>
<td>6.1 ±1.5</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Clinic visits with a Professional Nurse per patient</td>
<td>4.2 ±1.8</td>
<td>5.6 ±1.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clinic visits with an Enrolled Nurse per patient</td>
<td>0.9 ±0.9</td>
<td>0.4 ±0.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Number of viral load tests per patient</td>
<td>2.0 ±0.3</td>
<td>1.9 ±0.5</td>
<td>0.006</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cost per HIV viral load test</th>
<th>Point-of-care Test</th>
<th>Centralized Laboratory Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>$21.53</td>
<td>$25.98</td>
<td></td>
</tr>
<tr>
<td>Total over 5 years testing per patient</td>
<td>$129.18</td>
<td>$155.88</td>
</tr>
</tbody>
</table>
Dolutegravir Studies in Adults
12 Month Outcomes on DTG ART Botswana: The BEAT Cohort Study
Avalos A et al. CROI 2019 Seattle, WA Abs. 505

- Observational study, with data abstraction electronic national HIV and lab database from 11 urban and semi-rural facilities.
- Data on 2,256 adults: 1,523 ART-naïve, 638 ART-switch, 95 highly ART-experienced.
  - Median age 39 yr (range 32-48), 63% female
  - VL reporting in only 50 % (N=1134)
- 77 women in database pregnant (11 on DTG preconception), no NTD.

<table>
<thead>
<tr>
<th>Cohort</th>
<th>% with 12-Month Viral Load Measurements</th>
<th>% VL Suppression &lt;400 copies/mL with (95% CL) Overall and by gender.</th>
<th>Adverse Events % (#) (DAIDS—Grave 3)</th>
<th>LTFU % (#)</th>
<th>Deaths % (#)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naïve (n=1523)</td>
<td>41% (n=623)</td>
<td>Overall: 98.6% (97.3, 99.3)</td>
<td>&lt;1% (n=2)</td>
<td>6.3% (n=33)</td>
<td>1.9% (n=30)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Female: 98.8% Male: 98.2%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Switched (n=638)</td>
<td>70% (n=436)</td>
<td>Overall: 95.9% (94.8, 98.1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Female: 96.3% Male: 98.3%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Highly Treatment Experienced</td>
<td>79% (n=75)</td>
<td>Overall: 89.1% (77.3, 96.1)</td>
<td>1% (n=1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>(n=95)</td>
<td></td>
<td>Female: 90.1% Male: 86.4%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (n=2256)</td>
<td>50% (n=1134)</td>
<td>Overall: 97.4% (96.4, 98.2)</td>
<td>&lt;1% (n=3) Women: 2</td>
<td>1.4% (n=33) Women: 51.6%</td>
<td>1.3% (n=30) Men: 67%</td>
</tr>
</tbody>
</table>
Dolutegravir and Weight Gain

- **Lake J. Abs. 669:**
  - 972 adults switched to InSTI in A5001, A5322; median 7.8 yr prior ART
  - Women, black and age >60 most increase
  - DTG greatest weight gain

- **Bourgi K. Abs. 670:**
  - 24,001 ART naïve pts starting ART 2007-2016 (NNRTI 11,826; PI 7,436, InSTI 4,440)
  - ART naïve starting InSTI, esp DTG and RAL at risk of weight gain
  - No difference by sex and race

- **McComsey G. Abs. 671**
  - 3,468 pt with viral suppression and BMI measure at start and 1-2 years
  - >3% weight gain in 30%
  - Associated with lower/higher BMI baseline, non-PI regimen, psych disorder
  - InSTI not associated in multivariate
**Dolutegravir and Weight Gain**

- **Kerchberger AM. Abs. 672**
  - WIHS 2008-2017, evaluated weight in suppressed women who switched to InSTI or stayed on non-InSTI regimen
  - InSTI switch associated with significant ↑ body weight, BMI, total body fat, body circumference measure and blood pressure compared to staying on non-InSTI ART

- **Palella FJ. Abs. 674**
  - BMI data from 653 pt from HIV Outpatient Study (HOPS)
    - 368 (56%) switched to InSTI
    - 285 (44%) switched to non-InSTI
  - Weight gain was higher among InSTI switch, and was greatest with DTG (yellow)
  - Associated factors: female, Hispanic ethnicity
**Bedimo R. Abs. 675**

- Yearly change in BMI following initiation of PI or InSTI ART
- Change BMI greatest among women compared to men
- EVG and DTG had more BMI ↑ than PI
- Weight gain with EVG had did not vary by sex/ethnicity
- Weight gain with DTG greatest in women and black/hispanics
DTG vs LPV/r for Second-Line Therapy (DAWNING)
Viral Efficacy by Presence Baseline DR Mutations

Brown D et al. CROI 2019 Seattle, WA Abs.144

→ Failing 1\textsuperscript{st} line NNRTI
→ No resistance to PI/InSTI
→ At least 1 fully active NRTI (based on resistance testing)

Primary endpoint VL<50 week 48:

<table>
<thead>
<tr>
<th>Baseline Drug Resistance Mutations</th>
<th>M184 V/I overall</th>
<th>M184 V/I Alone</th>
<th>M184 V/I + ≥1 TAM</th>
<th>K65R</th>
<th>K70E</th>
<th>1 TAM</th>
<th>≥2 TAMs</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTG</td>
<td>84%</td>
<td>25%</td>
<td>59%</td>
<td>30%</td>
<td>11%</td>
<td>17%</td>
<td>6%</td>
</tr>
<tr>
<td>LPV/r</td>
<td>81%</td>
<td>27%</td>
<td>54%</td>
<td>29%</td>
<td>12%</td>
<td>20%</td>
<td>6%</td>
</tr>
</tbody>
</table>

Outcomes Overall and by Baseline Resistance Subgroups at Week 48

- **Overall results** show superior efficacy of DTG over LPV/r for 2\textsuperscript{nd} line ART.
- **Consistent with overall results**, VL response rates were high regardless of pre-existing resistance to one of the NRTIs in the background regimen, including when XTC used in presence of M184 V/I.
- **Rates viral failure lower** in DTG arm regardless of baseline NRTI resistance and 2\textsuperscript{nd} line background NRTI.
ARV Drug Resistance
Population-Based Monitoring of Pre-ART Drug Resistance, Eswatini
Khan S et al. CROI 2019 Seattle, WA Abs. 537

- Evaluated pre-treatment drug resistance in HIV+ ART-naïve adults enrolling in MaxART trial in Hhohho region Sept 2014-Aug 2017 (N=3485); testing done for 2578 (98%) available samples.

- Resistance seen in 24.1%, primarily driven by NNRTI resistance; 286 (11.1%) had mutations conferring resistance to 1st line NNRTI EFV/NVP.

- Dual class resistance to NNRTI and NRTI drugs was rare (14, 0.5%).

- NNRTI resistance associated with female gender (aOR 1.4, p=0.05) and younger age at ART start (aOR 0.96 per 1 year increment, p<0.01).

- Supports move to DTG as 1st line ART in Eswatini.
### HIV Drug Resistance, Population-Based Household Survey, South Africa

*Moyo S et al. CROI 2019 Seattle, WA Abs. 152*

- Cross-sectional population-based household survey 2017, including HIV testing and DBS resistance testing.
- 2,294 HIV+ → 2,246 VL result → 1,107 unsuppressed → 697 DR testing successful → 200 DR (27%), 497 no DR
- Primarily NNRTI resistance; dual resistance NNRTI/NRTI in 8%; low level resistance to 2\(^{nd}\) line.
- Drug resistance in more than half on treatment, 15% naïve; no difference by sex and age.

<table>
<thead>
<tr>
<th>Resistance</th>
<th>% weighted (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any resistance</td>
<td>27.4% (22.8-32.6)</td>
</tr>
<tr>
<td>NNRTI</td>
<td>18.9% (14.8-23.8)</td>
</tr>
<tr>
<td>NNRTI + NRTI</td>
<td>7.8% (5.6-10.9)</td>
</tr>
<tr>
<td>PI + NNRTI + NRTI</td>
<td>0.5% (0.1-2.1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>Any DRM (95% CI)</th>
<th>NNRTI only</th>
<th>NNRTI+NRTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARV status:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On ART</td>
<td>55.7% (42.6-67.9)</td>
<td>14.3% (7.5-25.6)</td>
<td>40.4% (29.6-52.2)</td>
</tr>
<tr>
<td>Defaulter*</td>
<td>75.9% (59.2-87.3)</td>
<td>56.4% (34.4-25.7)</td>
<td>14.3% (2.5-52.1)</td>
</tr>
<tr>
<td>ARV-naïve</td>
<td>15.3% (6.3-32.8)</td>
<td>15.3% (6.3-32.8)</td>
<td>0</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>29.4% (22.5-37.4)</td>
<td>19.6% (13.5-27.7)</td>
<td>9.7% (5.8-15.7)</td>
</tr>
<tr>
<td>Female</td>
<td>25.8% (19.8-32.8)</td>
<td>18.3% (13.2-24.8)</td>
<td>6.3% (4.2-9.5)</td>
</tr>
<tr>
<td>Age (years):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-14</td>
<td>33.7% (17.6-54.7)</td>
<td>17.7% (7.2-37.4)</td>
<td>14.9% (5.3-35.2)</td>
</tr>
<tr>
<td>15-24</td>
<td>30.5% (18.7-45.5)</td>
<td>22.1% (12.6-35.9)</td>
<td>5.7% (1.7-15.9)</td>
</tr>
<tr>
<td>25-49</td>
<td>26.6% (21.7-32.2)</td>
<td>18.6% (13.8-24.8)</td>
<td>8.2% (5.4-12.2)</td>
</tr>
<tr>
<td>50+</td>
<td>24.1% (14.8-36.7)</td>
<td>17.0% (8.9-30.0)</td>
<td>5.7% (2.5-12.8)</td>
</tr>
</tbody>
</table>

*Defaulter: stated were on ART but negative test ARV*
Modeling Impact of DTG Introduction on NNRTI Resistance, South Africa
Hauser A et al.  CROI 2019 Seattle, WA Abs. 538

- Epidemiologic modeling to investigate development of pre-ART NNRTI drug resistance (DR) under different scenarios of DTG introduction.

- Assumes DTG efficacy similar to NNRTI and dx and treatment rates constant from 2018.

- DTG to all pt regardless gender and treatment status results in lowest NNRTI resistance, 8.2%, in 2035.

- DTG limited to men (or men+women non-childbearing age) will not prevent increase in NNRTI DR to ~17% in 2035.

- Including men and women using contraception will stabilize resistance at 11.8%. 
U=U Symposium

UNDETECTABLE = UNTRANSMITTABLE

U=U refers to the concept that an individual with an undetectable HIV VL is incapable of transmitting their HIV infection to sexual partners.¹

Undetectable VL in this context: <200-400 c/ml

"People who take ART daily as prescribed and achieve and maintain an undetectable viral load have effectively no risk of sexually transmitting the virus to an HIV-negative partner." The U.S. Centers for Disease Control and Prevention (CDC) (September, 2017)

https://www.preventionaccess.org/undetectable
Provided scientific backdrop to U=U (undetectable in the studies defined as <200-400 c/mL).

- **So far:** not a single documented case of transmission during cART
- **Continued absence of evidence** is evidence
- All prospective studies evaluating the risk found zero risk!
- Even if risk is not zero, it is < 1:1000 PY
Proving the negative
Difficult but not impossible

“In some circumstances it can be safely assumed that if a certain event had happened, evidence of it could be discovered by qualified investigators.

In such circumstances, it is perfectly reasonable to take the absence of proof of its occurrence as positive proof of its non-occurrence”

Copi, *Introduction to Logic* (1953) pg 95
**Areas of Uncertainty:**

**MTCT:** Transmission seen in women with delivery VL <50 (who weren’t <50 when got pregnant)

**Breastfeeding:** PROMISE two postnatal transmissions with undetectable maternal VL

**For MTCT/BF, maybe U=U only if:**
Undetectable - when get pregnant, throughout pregnancy, at delivery, and throughout breastfeeding
Community Voice on U=U
Foote C.  CROI 2019 Seattle, WA Symposium

U=U IS a Game Changer

❤️ Transforms social, sexual, & reproductive lives.

⚠️ Dismantles HIV stigma.

💊 Encourages getting tested and starting and staying on treatment and in care.

📢 Provides a strong public health argument for eliminating barriers to universal access to care (e.g., the third U = Unequal Access).

Language Matters

"From a practical standpoint, the risk is zero."
(Dr. Anthony Fauci, NIAID)

Be clear and consistent about risk.

Say:
- Can’t pass it on
- Can’t transmit
- Effectively no risk
- No risk
- Zero risk
- Prevents HIV
- Eliminates onward transmission

Don’t say:
- Greatly reduces
- Extremely unlikely
- Nearly impossible
- Almost no risk
- Close to zero
- Helps prevent
- Makes it hard to transmit