Why can TAF and DTG solve some implementation problems in LMICs?

July 2017

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Wits Reproductive Health and HIV Institute

* Thanks Beatriz Grinsztejn
Disclosures...

- Part of optimisation collaborations – grants to improve testing, new drug regimens, linkage to care
- Pharma (including drug donations for studies) and managed care
### 2016 WHO ART Guidelines

<table>
<thead>
<tr>
<th>Preferred option</th>
<th>ARV regimen* †</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TDF + XTC‡+ EFV₆₀₀</strong></td>
<td></td>
</tr>
</tbody>
</table>

#### Alternative options

- **AZT + 3TC + EFV₆₀₀**
- **AZT + 3TC + NVP**
- **TDF + XTC‡+ NVP**

- **TDF + XTC‡+ DTG§**
- **TDF + XTC‡+ EFV₄₀₀§**

**DTG**=dolutegravir

*ARV regimens as fixed-dose combinations is the preferred approach because of clinical, operational, and programmatic benefits

†Countries should discontinue d4T use in first-line regimens because of its well-recognized metabolic toxicities

‡XTC = 3TC or FTC

§These alternative regimens are expected to be available only in 2017. Safety data PLHIV with TB co-infection and in HIV+ pregnant women still pending

• The international programme is doing well (from a drug choice perspective)! We need a lot of evidence to start tinkering with it

• Dolutegravir – potential game changer re resistance (and replace efavirenz)

• Tenofovir alafenemide (TAF)- lower dose, less toxic version of currently used tenofovir (TDF)
Summary indicators for CCMT M&E in SA - Adults

Period: from Q1 2012 to Q1 2015

Select Age Category: Adults

# People on treatment (DHIS)

- GP
- FS
- EC
- WC
- NW
- NC
- MP
- KZN
- LP

2,836,866

# People with a VL test done in the last 12 months

- GP
- FS
- EC
- WC
- NW
- NC
- MP
- KZN
- LP

2,146,853

% People in care and on ART with a VL <= 1000 copies/ml

81.9%

% People in care and on ART, who have a VL done at least annually

75.7%

% People with CD4 tests done, with a CD4 count <= 500 cells/mm3

69.3%

% People with CD4 tests done, with a CD4 count <= 350 cells/mm3

47.4%

% People with CD4 tests done, with a CD4 count <= 200 cells/mm3

23.9%

% People with CD4 tests done, with a CD4 count <= 100 cells/mm3

11.5%
Six-week and final mother-to-child transmission rates, by country, 2015

<table>
<thead>
<tr>
<th>Country</th>
<th>Six-week transmission rate</th>
<th>Final transmission rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angola</td>
<td>11.1</td>
<td>20.6</td>
</tr>
<tr>
<td>Chad</td>
<td>10.9</td>
<td>19.4</td>
</tr>
<tr>
<td>Ghana</td>
<td>7.9</td>
<td>17.7</td>
</tr>
<tr>
<td>Côte d’Ivoire</td>
<td>5.7</td>
<td>16.1</td>
</tr>
<tr>
<td>Democratic Republic of the Congo</td>
<td>4.6</td>
<td>15.2</td>
</tr>
<tr>
<td>Cameroon</td>
<td>5.2</td>
<td>12.6</td>
</tr>
<tr>
<td>Lesotho</td>
<td>5.2</td>
<td>11.0</td>
</tr>
<tr>
<td>Malawi</td>
<td>3.6</td>
<td>7.6</td>
</tr>
<tr>
<td>Kenya</td>
<td>4.8</td>
<td>8.3</td>
</tr>
<tr>
<td>United Republic of Tanzania</td>
<td>3.6</td>
<td>7.6</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>4.0</td>
<td>7.2</td>
</tr>
<tr>
<td>Burundi</td>
<td>3.2</td>
<td>6.7</td>
</tr>
<tr>
<td>Mozambique</td>
<td>3.0</td>
<td>6.2</td>
</tr>
<tr>
<td>Zambia</td>
<td>2.8</td>
<td>5.8</td>
</tr>
<tr>
<td>Namibia</td>
<td>1.7</td>
<td>4.1</td>
</tr>
<tr>
<td>Swaziland</td>
<td>1.7</td>
<td>3.3</td>
</tr>
<tr>
<td>Uganda</td>
<td>1.3</td>
<td>2.9</td>
</tr>
<tr>
<td>Botswana</td>
<td>2.1</td>
<td>2.6</td>
</tr>
<tr>
<td>South Africa</td>
<td>1.4</td>
<td>2.0</td>
</tr>
</tbody>
</table>

Source: UNAIDS 2016 estimates
~4 YEAR LAG BETWEEN SCALE UP OF ART AND DECLINE IN MTB INCIDENCE

Figure 1: Incidence of microbiologically-confirmed pulmonary tuberculosis (per 100,000 population) and antiretroviral treatment coverage rates in HIV-infected individuals nationally in South Africa nationally and provincially from 2004 to 2012

The solid black line represents the estimated trend in PTB incidence per 100,000 population over the study period and the dotted black line the corresponding 95% confidence interval. The overlaid dotted grey line is the ART coverage per 1000 HIV positive individuals based on data from the ASSA 2008 model.

ART discontinuation for AE

<table>
<thead>
<tr>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cessation (SD)</td>
<td>10% (7.9)</td>
<td>9-1% (6.4)</td>
<td>7-9% (4.6)</td>
<td>6-1% (3.5)</td>
<td>4-2% (2.4)</td>
</tr>
</tbody>
</table>

Do we have a resistance problem?

- PDR prevalence ~9% in both recently- and chronically infected participants
- 2x more low-level variants detected with NGS
- NNRTI mostly compromised by PDR, but NRTIs are still active

Mostly driven by K103N
TDF + XTC + EFV
AZT + XTC + PI (lopinavir or atazanavir)

XTC, other nukes
Darunavir, Raltegravir, Etravirine
Efavirenz

- Daily, cheap, co-formulated, huge experience base, TB (and most everything else)-friendly
- EFV side effects predictable, treatable, substitutions easy
- Increasing recognition of CNS side effects
- Rash, hepatitis, gynaecomastia, lipids
- 2016: serious and fatal rare CNS side effects, hepatic events
Depression

- **Efavirenz** (6%)
  - 2x higher risk for suicidality
- **Rilpivirine** (8%)
- **Elvitegravir/COBI** (5%)
- **Raltegravir** (6%)
- **Atazanavir/r** (2%)


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**Meta-analysis**

\[ n=5332, 4 \text{ RCT} \]

\[ \text{Cumulative Incidence} \]

- **Gray } P = 0.005**
- For composite endpoint
- ‘Only’ trend for completed/attempted suicide (17 events occurred)

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**Lack of association between use of efavirenz and death from suicide: evidence from the D:A:D study**

#O315 Wednesday 5 November

C. Smith; L. Ryom; A. d’Arminio Monforte; P. Reiss; A. Mocroft; W. El-Sadr; R. Weber; M. Law; C. Sabin; J. Lundgren.

TDF + XTC + DTG

AZT + 3TC + PI (lopinavir or atazanavir)

XTC, other nukes

Darunavir, Raltegravir, Etravirine
DTG near unbreakable....

• And cheaper than EFV is many countries!
• Very well tolerated
**Integrase inhibitors and IRIS**

- Results from the Athena cohort that integrase inhibitors use in HIV-1 late presenters is an independent risk factor for IRIS.

- Data from the French Dat’AIDS cohort show higher risk for IRIS among individuals who started ART with a integrase-based regimen.

- Case reports emerging from Botswana and the UK of TB-IRIS with first-line with integrase-based treatment.

- This could increase the burden on health care workers and hospital/ clinical costs.

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Hoffman et al. HIV Medicine (2017), 18, 56-63
Libre et al. CROI 2017 abstract# 651

Wilking et al. CROI 2017 – abstract# 731
Deterer et al. CROI 2017 – abstract# 732
Personal communication Anton Petrizky
TAF

• Safer (laboratory)
• Cheaper than TDF
But

- TAF and DTG are made by commercial competitors
- Need data before moving millions of people over
# New Studies with DTG & TAF in PLHIV

(Adults & Children)

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Intervention</th>
<th>Major outcomes</th>
<th>N</th>
<th>Study Countries</th>
<th>Expected Completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAMSAL</td>
<td>DTG</td>
<td>Safety / efficacy of DTG vs EFV in initial ART of PLHIV in RLS (TDF/3TC + DTG vs TDF/3TC + EFV)</td>
<td>VL at 24 and 48 weeks, CD4 changes, disease progression, treatment discontinuation, AEs; HIVDR, time to viral suppression</td>
<td>606</td>
<td>Cameroon</td>
<td>Q3 2018</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>DTG</td>
<td>Safety / efficacy of DTG and TAF in initial ART (TDF + FTC + DTG vs TAF + FTC + DTG vs TDF + FTC + EFV)</td>
<td>VL at 24 and 48 weeks, CD4 changes, disease progression, treatment discontinuation, AEs; HIVDR,</td>
<td>1050</td>
<td>South Africa</td>
<td>Q4 2019</td>
</tr>
<tr>
<td>DAWNING</td>
<td>DTG</td>
<td>Safety / efficacy of DTG vs LPV/r in PLHIV failing 1st line ART (2NRTI + DTG vs 2NRTI + LPV/r)</td>
<td>VL at 96 weeks, CD4 changes, disease progression, treatment discontinuation,</td>
<td>612</td>
<td>Argentina, Brazil, Chile, China, Colombia, Kenya, Mexico, Peru, Romania, Russia, South Africa, Thailand, Ukraine</td>
<td>Q4 2018</td>
</tr>
<tr>
<td>ODYSSEY</td>
<td>DTG</td>
<td>2NRTI + DTG vs Soc in children/ young adults (6-18 yrs) with HIV starting 1st line or switching to 2nd line ART</td>
<td>VL at 24 and 48 weeks, CD4 changes, disease progression, treatment discontinuation, AEs</td>
<td>700</td>
<td>Argentina, Austria, Belgium, Brazil, Denmark, France, Ireland, Germany, Italy, Netherlands, Poland, Portugal, Romania, Spain, Sweden, Switzerland, Thailand, Uganda, UK, Ukraine, USA</td>
<td>Q3 2019</td>
</tr>
<tr>
<td>ARIA</td>
<td>DTG</td>
<td>Safety / efficacy of DTG vs ARTV/r in initial ART of women with HIV (ABC/3TC/DTG vs TDF/3TC + ATV/r)</td>
<td>VL at 24 and 48 weeks, CD4 changes, disease progression, treatment discontinuation, AEs HIVDR,</td>
<td>495</td>
<td>Belgium, Dominican Republic, France, Italy, Mexico, Portugal, Puerto Rico, Russia, Thailand, Uganda, UK, USA</td>
<td>Q4 2020</td>
</tr>
<tr>
<td>Study</td>
<td>Drug</td>
<td>Intervention</td>
<td>Major outcomes</td>
<td>N</td>
<td>Study Countries</td>
<td>Expected Completion</td>
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<tr>
<td>SSAT 062</td>
<td>EFV</td>
<td>EFV 400 mg pK in PLHIV in presence of RIF and INH, with and without TB</td>
<td>pK data, AEs, treatment discontinuation, influence of genetic polymorphism and EFV exposure</td>
<td>35</td>
<td>Uganda and UK</td>
<td>Q2 2017</td>
</tr>
<tr>
<td>INSPIRING (ING117175)</td>
<td>DTG</td>
<td>Safety /efficacy of DTG vs EFV in PLHIV with TB confection using RIF (50 mg DTG twice daily vs 600 mg EFV once daily during TB treatment)</td>
<td>VL at 24 and 48 weeks, CD4 changes, treatment discontinuation, AEs; HIVDR</td>
<td>125</td>
<td>Argentina, Brazil, Mexico, Peru, Russian Federation, South Africa, Thailand</td>
<td>Q4 2017</td>
</tr>
<tr>
<td>SSAT 075</td>
<td>TAF</td>
<td>TAF and TDF pK in presence of RIF (HIV negative patients)</td>
<td>TDF DP levels</td>
<td>20</td>
<td>South Africa</td>
<td>Q4 2017</td>
</tr>
</tbody>
</table>
### New ARVs in Pregnancy: Current Studies

**Study** | **Drug** | **Intervention** | **Major outcomes** | **N** | **Study Countries** | **Expected Completion**
--- | --- | --- | --- | --- | --- | ---
SSAT 063 | EFV<sub>400</sub> | EFV 400mg pK and safety in pregnant women with HIV using ARV regimen containing EFV at standard dose | pK data 3<sup>rd</sup> trimester and post partum; maternal and infant AEs; adverse pregnancy outcomes; genetic polymorphisms influence on EFV pK | 25 | Uganda, UK | Q2 2017
DOLPHIN 1 | DTG | DTG pK in pregnant women with HIV | pK data in 3<sup>rd</sup> trimester and 2 weeks postpartum; maternal VL at delivery | 60 | South Africa, Uganda | Q4 2017
DOLPHIN 2 | DTG | DTG safety/efficacy/ tolerability in pregnant women with HIV | pK data 3<sup>rd</sup> trimester and 18 weeks post partum, maternal VL at delivery, breast milk sterilization | 250 | South Africa, Uganda | Q1 2021
ING200336 | DTG | DTG pK and safety in unintended pregnancies in ARIA study (DTG/ABC/3TC vs ATV/r+ TDF/FTC) | pK data in 2<sup>nd</sup> and 3<sup>rd</sup> trimester; pK in neonates, maternal and infant adverse events; adverse pregnancy outcomes, maternal disease progression and fetal transmission | 25 | Spain, Russia, UK, USA | Q1 2019
WAVES OLE | TAF | TAF safety/efficacy/ tolerability in pregnant women with HIV (TAF/FTC/EVGc vs ATV/r +TDF/FTC) | Maternal VL at 48 weeks | 583 | Belgium, Dominican Republic, France, Italy, Mexico, Portugal, Puerto Rico, Russia, Thailand, Uganda, USA | Q2 2017
IMPAACT P1026s | DTG TAF | DTG and TAF pK in women with HIV on ART > 20 weeks of pregnancy and post partum | pK data (during pregnancy and post partum), pK data in neonates, maternal:cord blood ration, maternal and infant AEs, adverse pregnancy outcomes | 100 | Argentina, Botswana, Brazil, Puerto Rico, South Africa, Thailand, Uganda, USA | Q3 2017
IMPAACT P2010 | DTG TAF | DTG and TAF safety/efficacy in women with HIV starting ART at 14-28 weeks of pregnancy (DTG+ TAF/FTC vs DTG/TDF/FTC vs EFV/TDF/XTC) | Maternal VL at delivery, adverse pregnancy outcomes, maternal toxicity, SAB, foetal deaths, infant AEs, mother-infant ARV transfer at birth and from breast milk | 549 | Argentina, Botswana, Brazil, Puerto Rico, South Africa, Tanzania, Thailand, USA, Zimbabwe | Q3 2018
PANNA | DTG TAF | DTG and TAF safety/efficacy in women with HIV receiving ART and < 33 weeks of pregnancy | PK data in week 33 of pregnancy and 4-6 weeks after delivery, pK data in neonates; maternal VL and fetal transmission; maternal and infant AEs; adverse pregnancy outcomes | 32 | Belgium, Germany, Ireland, Italy, Netherlands, Spain, UK | Q4 2020
<table>
<thead>
<tr>
<th>Clinical trials: Children and adolescents</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase</strong></td>
</tr>
<tr>
<td>------------------</td>
</tr>
<tr>
<td>GS-US-183-0160</td>
</tr>
<tr>
<td>CR108265</td>
</tr>
<tr>
<td>GS-US-292-1515</td>
</tr>
<tr>
<td>GS-US-236-0112</td>
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<tr>
<td>IMPAACT P1093</td>
</tr>
<tr>
<td>ING114916</td>
</tr>
<tr>
<td>SMILE (PENTA 17)</td>
</tr>
<tr>
<td>GS-US-380-1474</td>
</tr>
<tr>
<td>ODYSSEY (PENTA 20)</td>
</tr>
<tr>
<td>GS-US-311-1269</td>
</tr>
<tr>
<td>GS-US-216-0128</td>
</tr>
<tr>
<td>GS-US-292-0106</td>
</tr>
<tr>
<td>IMPAACT 2006*</td>
</tr>
</tbody>
</table>

Clinicaltrials.gov *www.impaactnetwork.org/studies
What is the cost if we switch to DTG/TAF?

- Millions of patients will need to be switched (assuming stable patients on EFV will move, seems likely) – huge undertaking – and the manufacturing changes will likely be slightly chaotic.
- Moving from EFV to DTG unlikely to be a big deal (?VL); reverse a problem.
- TAF to TDF not an issue.
- ?harmonisation between and within different countries.
- Pregnancy – limited data.
- TB – studies are needed.
- Studies largely done in men.
- Hep B = major problem when considering DTG/3TC dual therapy.
So…

• DTG may mean second and subsequent regimens are unusual – huge implications for focus on VL and adherence and genotyping

• May mean we can transition all second line back to first

• TAF very important for cost, long-term toxicity

• Hep B a constant challenge; hep C coming
Thank you
USAID, UNITAID, WHO, HIV i-Base, CHAI, Mylan, ICAP, MPP, Andrew Hill, Anton Pozniak, Marta Boffito, Michelle Moorhouse
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