Can we improve first-line and second-line ART?

Presented by Dr Tom Boyles
Developed by Prof Francois Venter
Wits Reproductive Health and HIV Institute

Slide acknowledgements: Beatriz Grinsztejn, Joe Eron, WHO, UNAIDS, Clinical Care Options, CHAI, Celicia Serenata, Charley Flexner and others
Disclosures...

• Part of optimisation collaborations – grants to improve testing, new drug regimens, linkage to care

• Pharma (including drug donations for studies) and managed care
HIV and South Africa
Before and after initiation of ARV therapy!
Before and after initiation of ARV therapy!

Thapelo
South Africa: Why is it important? (and why is it different)?

- Size of the country – 51 million people (2011), 5th largest in Africa
- Wealth – highest GDP in Africa, best infrastructure
- Size of HIV and TB problem
SA snapshot

- 3.4 million 1\textsuperscript{st} line ($110/year)
- 145,000 2\textsuperscript{nd} line ($350/year)
- 700 3\textsuperscript{rd} line (roughly $1500/year, depends on regimen ($2000 if DRV/DTG/ETR))
- Bill 2014/2015: $350 million
- Sept 2016: Test and treat – theoretically doubling numbers
- SA drives the global market

[SA=PEPFAR=Global Fund by ART volume]
Incidence still remains stubbornly high...
Country status
Progress toward the 90–90–90 targets, all ages, by country, 2015

Knowledge of status among people living with HIV (%)
Coverage of antiretroviral therapy among people living with HIV (%)
Viral suppression among people living with HIV (%)

Legend
- 90% and higher
- 81% or higher
- 73% and higher
- 45–89%
- 41–80%
- 37–72%
- 44% or lower
- 40% or lower
- 36% or lower
- Measures not available

• Uganda/US/UK – ‘higher life expectancy that matched populations

1. Expect a normal life expectancy:
   May et al. AIDS 2014

   • UK CHIC: 21 388 people started ART 2000-2010

   If 35 year old man started ART:

<table>
<thead>
<tr>
<th>CD4</th>
<th>Baseline</th>
<th>1 year ART</th>
<th>5 years ART</th>
<th>&amp; VL&gt;50</th>
<th>&amp; VL&lt;50</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;200</td>
<td>71</td>
<td>71</td>
<td>71</td>
<td>S4</td>
<td>S4</td>
</tr>
<tr>
<td>200-349</td>
<td>78</td>
<td>78</td>
<td>78</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;350</td>
<td>77</td>
<td>81</td>
<td>81</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

   General population 78

   Conclusion: If diagnosed, in care and on effective ART: life expectancy is normal.

   Great information to give to people newly diagnosed and encourage good adherence.

Thanks: Julie Fox, Guys
When to start debate solved in 2015: thanks to safer drugs

Table 1: Severe morbidity in TEMPRANO study at 30 months

<table>
<thead>
<tr>
<th>Group</th>
<th>% events</th>
<th>n</th>
<th>Rate / 100 PY</th>
<th>adj HR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO ART</td>
<td>11.4%</td>
<td>111</td>
<td>4.9</td>
<td>0.56</td>
<td>0.0002</td>
</tr>
<tr>
<td>Early ART</td>
<td>6.6%</td>
<td>64</td>
<td>2.8</td>
<td>0.56</td>
<td>0.0002</td>
</tr>
<tr>
<td>No IPT</td>
<td>10.7%</td>
<td>104</td>
<td>4.7</td>
<td>0.65</td>
<td>0.005</td>
</tr>
<tr>
<td>IPT</td>
<td>7.2%</td>
<td>71</td>
<td>3.0</td>
<td>0.65</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Table 1. Primary endpoint and its components in open DSMB report (15 May 2015)

<table>
<thead>
<tr>
<th>Component</th>
<th>Early ART (arm A)</th>
<th>Deferred ART (arm B)</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS, serious non-AIDS, or death (primary)</td>
<td>41</td>
<td>86</td>
<td>0.47 (0.32 to 0.68)</td>
</tr>
<tr>
<td>AIDS or AIDS death</td>
<td>14</td>
<td>16</td>
<td>0.30 (0.17 to 0.55)</td>
</tr>
<tr>
<td>Serious non-AIDS or non-AIDS death</td>
<td>28</td>
<td>41</td>
<td>0.67 (0.42 to 1.09) NS**</td>
</tr>
</tbody>
</table>

* PY = patient years, ** NS = non significant

Thanks: Simon Collins
Is sex safe? HPTN 052

And confirmed in Partners study

HR = 0.37 or 96.3% reduction in transmission
Number of people living with HIV (aged 50 years and over), high-income countries and low- and middle-income countries, 2000–2015 and projected to 2020

Source: UNAIDS 2016 estimates. Note: Projections 2016–2020 are based on an assumption that scale up of antiretroviral treatment will reach 81% coverage of all people living with HIV by 2020. Country income classifications are from 2015.
Investments in the AIDS responses of low- and middle-income countries, by source of funding, 2000–2015

People living with HIV on antiretroviral therapy, all ages, global, 2010–July 2016

Distribution of antiretroviral therapy, by country, 2015

The Fast-Track countries include the 10 displayed on this chart, plus Angola, Botswana, Brazil, Cameroon, Chad, China, Côte d’Ivoire, Democratic Republic of the Congo, Ethiopia, Ghana, Haiti, Indonesia, Iran (Islamic Republic of), Jamaica, Lesotho, Malawi, Mali, Myanmar, Namibia, Pakistan, South Sudan, Swaziland, Russian Federation, Ukraine and Viet Nam.

Sources: GARPR 2016; UNAIDS 2016 estimates
Impact of HIV response on life expectancy

Dramatic impact of HIV response on life expectancy, 1950-2015

Aging with HIV infection-Athena Cohort

Non-communicable comorbidities

Burden of co-medications

HIV Pts More Likely to Experience Bone Fractures, CVD, Diabetes, Renal Failure


Slide credit: clinicaloptions.com
Science evolved: smarter and better HIV treatment options are now available

Drug optimization

Treatment 2019: One tablet smaller than an aspirin
We need things to go faster
### WHO ARV Guidelines Evolution 2002 to 2015

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</thead>
<tbody>
<tr>
<td><strong>When to start</strong></td>
<td>CD4 ≤200</td>
<td>CD4 ≤200</td>
<td>CD4 ≤200</td>
<td>CD4 ≤350</td>
<td>CD4 ≤500</td>
<td>CD4 ≤500 as priority</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Consider 350</td>
<td>Regardless CD4</td>
<td>Regardless CD4</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>− for tuberculosis (TB)</td>
<td>for TB and hepatitis B virus (HBV)</td>
<td>CD4 ≤350</td>
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<td></td>
<td></td>
<td></td>
<td>− Regardless CD4</td>
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<td>− Regardles CD4</td>
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<td>− CD4 ≤350</td>
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<td>− CD4 ≤350 as priority</td>
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<td>− Regardless CD4</td>
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<td></td>
<td></td>
<td>− CD4 ≤350</td>
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<tr>
<td><strong>First-Line ART</strong></td>
<td>8 options</td>
<td>4 options</td>
<td>8 options</td>
<td>6 options and FDCs</td>
<td>1 preferred option</td>
<td></td>
</tr>
<tr>
<td></td>
<td>− AZT preferred</td>
<td>− AZT preferred</td>
<td>− AZT or TDF preferred</td>
<td>− AZT or TDF preferred</td>
<td>and FDCs</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>− d4T dose reduction</td>
<td>− d4T dose reduction</td>
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<td></td>
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<td></td>
<td>− d4T phase out</td>
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<tr>
<td><strong>Second-Line ART</strong></td>
<td>Boosted and</td>
<td>Boosted PIs</td>
<td>Boosted Pl</td>
<td>Boosted Pl</td>
<td>Boosted PIs</td>
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<tr>
<td></td>
<td>non-boosted</td>
<td>− IDV/r LPV/r,</td>
<td>− ATV/r, DRV/r,</td>
<td>− Heat stable FDC:</td>
<td>− Heat stable FDC:</td>
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<tr>
<td></td>
<td>PIs</td>
<td>SQV/r</td>
<td>FPV/r LPV/r</td>
<td>ATV/r, LPV/r</td>
<td>ATV/r, LPV/r</td>
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<tr>
<td><strong>Third-Line ART</strong></td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>DRV/r, RAL, ETV</td>
<td>DRV/r, RAL, ETV</td>
<td></td>
</tr>
<tr>
<td><strong>Viral Load (VL) Testing</strong></td>
<td>No (desirable)</td>
<td>No (desirable)</td>
<td>Yes (tertiary centers)</td>
<td>Yes (phase-in approach)</td>
<td>Yes (preferred for monitoring, use of PoC, DBS)</td>
<td></td>
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<tr>
<td><strong>Earlier initiation</strong></td>
<td></td>
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<td><strong>Simpler treatment</strong></td>
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<td><strong>Less toxic, more robust regimens</strong></td>
<td></td>
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<tr>
<td><strong>Better and simpler monitoring</strong></td>
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</table>

- **Toward Treat All adolescents age band**
- **Continue with FDC and harmonization across age bands**
- **Greater number of options**
- **Encourage HIV DR to guide**
- **Support for scale up of VL using all technologies**
Do we have a resistance problem?
Global epidemiology of drug resistance after failure of WHO recommended first-line regimens for adult HIV-1 infection: a multicentre retrospective cohort study

The TenoRes Study Group

Summary

Background Antiretroviral therapy (ART) is crucial for controlling HIV-1 infection through wide-scale treatment as endorsed by the Joint United Nations Programme on HIV/AIDS (UNAIDS). Success of such efforts relies on effective initial ART regimens that delay development of drug resistance. Global HIV-1 drug resistance surveillance is essential for guiding the development and implementation of effective ART therapy.
“Researchers at University College London said the study could mean that, after a year of treatment, up to 15% of people in sub-Saharan Africa and 10% in South Africa were resistant to the drug.”
Resistance IS a problem....
Pretreatment Drug Resistance in TASP trial

Prevalence of PDR in TASP

- 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

Distribution of Drug Resistance Mutations per ARV class in all ART-naive

Mostly driven by K103N

*include only NGS data
Genetic Barrier to Resistance for Specific ARVs

<table>
<thead>
<tr>
<th>ARV regimen* †</th>
<th>Preferred option</th>
<th>Alternative options</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF + XTC‡+ EFV&lt;sub&gt;600&lt;/sub&gt;</td>
<td>AZT + 3TC + EFV&lt;sub&gt;600&lt;/sub&gt;</td>
<td>NEW TDF + XTC‡ + DTG§</td>
</tr>
<tr>
<td></td>
<td>AZT + 3TC + NVP</td>
<td>NEW TDF + XTC‡ + EFV&lt;sub&gt;400&lt;/sub&gt;§</td>
</tr>
<tr>
<td></td>
<td>TDF + XTC‡ + NVP</td>
<td></td>
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</tbody>
</table>

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

What are the requirements for an ideal regimen?

- Efficacy
- Safety and tolerability
- Convenience
- Special populations
  - HIV/TB
  - Pregnant women
  - Children/Adolescents
  - Acute infection
  - Aging
- Access
- Global Affordability
1\textsuperscript{st} line....

TDF + XTC + EFV

Cost driver

Side effect (and size) driver, resistance weak link
TDF + XTC + EFV

AZT + XTC + PI (lopinavir or atazanavir)

XTC, other nukes

Darunavir, Raltegravir, Etravirine
Tenofovir has taken over the world!

- 1st line recommendation by WHO; feature in EVERY guideline (some have ABC)
- Well tolerated, FDCs galore, daily
- Cheap (only alternative that is cheaper is d4T)
- Hep B for free
- Renal, bone concerns
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
BUT...

- Rash, hepatitis, gynaecomastia, lipids
- 2016: serious and fatal rare CNS side effects, hepatic events
- ENCORE (Lancet 2013): 400mg vs. 600mg
Depression

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

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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.

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EFV 400mg

- Studies currently underway – pregnancy and TB
- Likely results: 2017
- Then, probable mass switch to 400mg; cost saving ≈ 5-10%
- Other option: rilpivirine: but TB, VL, food issues
ART discontinuation for AE

The Integrase inhibitor era!

In CNICS cohort integrase inhibitor use was strongly associated with HIV RNA suppression

Thanks Joe Eron
What about: Dolutegravir

• (raltegravir and elvitegravir expensive)
• Wunderkind of the moment – almost unbreakable!
• 50mg once-daily (in naïve patients)
• Very good efficacy
• Minimal toxicity – but NEW data re CNS
• Pregnancy category B
• Potential to be low cost and co-formulated
## EFV 600 vs. DTG

<table>
<thead>
<tr>
<th>Major parameters</th>
<th>EFV 600</th>
<th>DTG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occurrence of SAEs</td>
<td>comparable</td>
<td></td>
</tr>
<tr>
<td>Better virologic suppression</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Better CD4 recovery</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Less treatment discontinuation</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Less occurrence of subjective side effects</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Lower potential for drug–drug interactions</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Efficacy in HIV-2 infection</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Efficacy in <strong>TB coinfection</strong></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Efficacy and safety in <strong>pregnant/breastfeeding women</strong></td>
<td>✓</td>
<td>?</td>
</tr>
<tr>
<td>Availability as <strong>generic formulations</strong></td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>
In US and EU, DTG-based regimens have become the top prescribed ARVs, affirming DTG’s clinically superior profile.

**US Weekly Treatment Market Share Since DTG Launch**

- In Feb 2013, the US Health and Human Services Guidelines on ARVs recommends INSTI-based regimens as the preferred for ART-naïve patients.
  - EFV no longer included in DHHS guidelines
- As of 2Q16, DTG treatment volume of >21,000 patients weekly, with nearly 1 in 5 patients on a DTG regimen in the US.
- DTG now leads US/EU markets:
  - US: #1 core agent in treatment share and volume
  - EU: #2 prescribed regimen in treatment-naïve patients

**The US and EU has long moved on from EFV-based treatment**

Source: GILD and GSK earnings.
Note: Graph depicts single tablet regimen plus core agent market.
Dolutegravir: discontinuation due to AE
Germany (2 cohorts), 1950 INSTI-based therapies

Discontinuation due to neuropsychiatric AE

Factors associated with DTG discontinuation

<table>
<thead>
<tr>
<th></th>
<th>RH</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female, vs. male gender</td>
<td>2.81</td>
<td>1.46–5.41</td>
<td>0.002</td>
</tr>
<tr>
<td>Older age (&gt; 60 years), vs. younger age</td>
<td>2.88</td>
<td>1.56–5.34</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ABC with DTG initiated, vs. no ABC</td>
<td>2.63</td>
<td>1.61–4.29</td>
<td>0.0001</td>
</tr>
<tr>
<td>DTG start in 2016, vs. in 2014/2015</td>
<td>8.93</td>
<td>3.76–21.28</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Neuropsychiatric AEs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female, vs. male gender</td>
<td>2.64</td>
<td>1.23–5.65</td>
<td>0.01</td>
</tr>
<tr>
<td>Older age (&gt; 60 years), vs. younger age</td>
<td>2.86</td>
<td>1.42–5.77</td>
<td>0.003</td>
</tr>
<tr>
<td>ABC with DTG initiated, vs. no ABC</td>
<td>2.42</td>
<td>1.38–4.24</td>
<td>0.002</td>
</tr>
<tr>
<td>DTG start in 2016, vs. in 2014/2015</td>
<td>11.36</td>
<td>4.31–29.41</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

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

Hsu et al CROI 2017 abstract# 664
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.

Wijting et al. Croi 2017 – abstract# 731
Dutertre et al. Croi 2017 - abstract #732
Personal communication Anton Pozniak
Cutting the cost of South African antiretroviral therapy using newer, safer drugs

W D F Venter, FCP (SA), MMed; B Kaiser, MPH, PharmD, BCPS; Y Pillay, PhD; F Conradie, MB BCh; G B Gomez, PhD; P Clayden, M Matsolo, C Amole, BA; I Rutter, BA; F Abdullah, MB ChB; FCHM; BSc Hons (Eni); F I Abrams, MD; C P Casas, MSc;
M Barnhart, MD, MPH; A Pillay, PhD; A Pozniak, MD, FR M Moorhouse, MB BCh; M Chersich, MB BCh, PhD; C Seren

1Wits Reproductive Health and HIV Institute, University of the Wit
2Formerly UNITAID, Geneva, Switzerland
3HIV/AIDS, TB and Maternal-Child and Women’s Health in the S

Fig. 2. Estimated crude savings on antiretroviral drugs (assuming implementation of new regimen in 2019 - 2020). Cumulative savings compared with status quo (conservative = 300 000 annually, transition from old regimen to new over 3 years; moderate = new regimen, 400 000 annually, transition over 2 years; aggressive = new regimen, 500 000 annually, transition over 1 year).
Phase 2 Bictegravir or Dolutegravir with FTC/TAF for Initial HIV Therapy
Virologic Outcomes at Weeks 24 and 48 by FDA Snapshot

<table>
<thead>
<tr>
<th></th>
<th>Week 24</th>
<th>Week 48</th>
</tr>
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<tbody>
<tr>
<td>Virologic Success</td>
<td>97/63</td>
<td>97/63</td>
</tr>
<tr>
<td>Virologic Failure</td>
<td>94/31</td>
<td>91/30</td>
</tr>
<tr>
<td>No Data</td>
<td>2/65</td>
<td>2/30</td>
</tr>
<tr>
<td>n=</td>
<td>65/33</td>
<td>65/33</td>
</tr>
</tbody>
</table>

% Treatment Difference (95% CI)

No resistance to study medications was detected in either arm

Sax P et al CROI 2017 abstract# 41
## Safety and Efficacy of INSTIs and EFV<sub>400</sub> in First-Line ART (NMA)

<table>
<thead>
<tr>
<th>Major outcomes</th>
<th>INSTI vs. EFV&lt;sub&gt;600&lt;/sub&gt;</th>
<th>DTG vs. other INSTI</th>
<th>DTG vs. EFV&lt;sub&gt;600&lt;/sub&gt;</th>
<th>DTG vs. EFV&lt;sub&gt;400&lt;/sub&gt;</th>
<th>EFV&lt;sub&gt;400&lt;/sub&gt; vs. EFV&lt;sub&gt;600&lt;/sub&gt;</th>
<th>Quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral suppression</td>
<td>INSTI better</td>
<td>DTG better</td>
<td>DTG better</td>
<td>comparable*</td>
<td>comparable</td>
<td>moderate</td>
</tr>
<tr>
<td>CD4 recovery</td>
<td>INSTI better</td>
<td>DTG better</td>
<td>DTG better</td>
<td>comparable</td>
<td>EFV&lt;sub&gt;400&lt;/sub&gt; better</td>
<td>moderate</td>
</tr>
<tr>
<td>Treatment discontinuation</td>
<td>INSTI better</td>
<td>DTG better</td>
<td>DTG better</td>
<td>comparable</td>
<td>EFV&lt;sub&gt;400&lt;/sub&gt; better</td>
<td>moderate</td>
</tr>
<tr>
<td>Mortality</td>
<td>comparable</td>
<td>comparable</td>
<td>comparable</td>
<td>comparable</td>
<td>comparable</td>
<td>low</td>
</tr>
<tr>
<td>AIDS progression</td>
<td>comparable</td>
<td>comparable</td>
<td>comparable</td>
<td>comparable</td>
<td>comparable</td>
<td>low</td>
</tr>
<tr>
<td>SAE</td>
<td>comparable</td>
<td>comparable</td>
<td>comparable</td>
<td>comparable</td>
<td>comparable</td>
<td>moderate</td>
</tr>
</tbody>
</table>

*Estimated effects favored DTG, but statistical analysis not significant

## New ARVs and TB drugs: Current Studies

<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>SSAT 062</td>
<td>EFV$\text{_{400}}$</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>
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<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>
<tr>
<td>Study</td>
<td>Drug(s)</td>
<td>Intervention</td>
<td>Major outcomes</td>
<td>N</td>
<td>Study Countries</td>
<td>Expected Completion</td>
</tr>
<tr>
<td>--------------</td>
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<td>-------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>-------</td>
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<td>---------------------</td>
</tr>
<tr>
<td>SSAT 063</td>
<td>EFV₈₀₀</td>
<td>EFV 400mg pK and safety in pregnant women with HIV using ARV regimen containing EFV at standard dose</td>
<td>pK data 3rd trimester and post partum; maternal and infant AEs, adverse pregnancy outcomes; genetic polymorphisms influence on EFV pK</td>
<td>25</td>
<td>Uganda, UK</td>
<td>Q2 2017</td>
</tr>
<tr>
<td>DOLPHIN 1</td>
<td>DTG</td>
<td>DTG pK in pregnant women with HIV</td>
<td>pK data in 3rd trimester and 2 weeks postpartum; maternal VL at delivery</td>
<td>60</td>
<td>South Africa, Uganda</td>
<td>Q4 2017</td>
</tr>
<tr>
<td>DOLPHIN 2</td>
<td>DTG</td>
<td>DTG safety/efficacy/ tolerability in pregnant women with HIV</td>
<td>pK data 3rd trimester and 18 weeks post partum, maternal VL at delivery, breast milk sterilization</td>
<td>250</td>
<td>South Africa, Uganda</td>
<td>Q1 2021</td>
</tr>
<tr>
<td>ING200336</td>
<td>DTG</td>
<td>DTG pK and safety in unintended pregnancies in ARIA study (DTG/ABC/3TC vs ATV/r + TDF/FTC)</td>
<td>pK data in 2nd and 3rd trimester; pK in neonates, maternal and infant adverse events; adverse pregnancy outcomes, maternal disease progression and fetal transmission</td>
<td>25</td>
<td>Spain, Russia, UK, USA</td>
<td>Q1 2019</td>
</tr>
<tr>
<td>WAVES OLE</td>
<td>TAF</td>
<td>TAF safety/efficacy/ tolerability in pregnant women with HIV (TAF/FTC/EVGc vs ATV/r +TDF/FTC)</td>
<td>Maternal VL at 48 weeks</td>
<td>583</td>
<td>Belgium, Dominican Republic, France, Italy, Mexico, Portugal, Puerto Rico, Russia, Thailand, Uganda, USA</td>
<td>Q2 2017</td>
</tr>
<tr>
<td>IMPACT P1026s</td>
<td>DTG TAF</td>
<td>DTG and TAF pK in women with HIV on ART &gt; 20 weeks of pregnancy and post partum</td>
<td>pK data (during pregnancy and post partum), pK data in neonates, maternal:cord blood ration, maternal and infant AEs, adverse pregnancy outcomes</td>
<td>100</td>
<td>Argentina, Botswana, Brazil, Puerto Rico, South Africa, Thailand, Uganda, USA</td>
<td>Q3 2017</td>
</tr>
<tr>
<td>IMPACT P2010</td>
<td>DTG TAF</td>
<td>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)</td>
<td>Maternal VL at delivery, adverse pregnancy outcomes, maternal toxicity, SAB, foetal deaths, infant AEs, mother-infant ARV transfer at birth and from breast milk</td>
<td>549</td>
<td>Argentina, Botswana, Brazil, Puerto Rico, South Africa, Tanzania, Thailand, USA, Zimbabwe</td>
<td>Q3 2018</td>
</tr>
<tr>
<td>PANNA</td>
<td>DTG TAF</td>
<td>DTG and TAF safety/efficacy in women with HIV receiving ART and &lt; 33 weeks of pregnancy</td>
<td>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</td>
<td>32</td>
<td>Belgium, Germany, Ireland, Italy, Netherlands, Spain, UK</td>
<td>Q4 2020</td>
</tr>
</tbody>
</table>
### Clinical trials: Children and adolescents

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Phase</th>
<th>Regimen</th>
<th>Age</th>
<th>Expected completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>GS-US-183-0160 (NCT01923311)</td>
<td>II/III</td>
<td>EVG/r</td>
<td>Up to 17 years</td>
<td>Q1 2017</td>
</tr>
<tr>
<td>CR108265 (NCT02993237)</td>
<td>I</td>
<td>DRV/c swallowing tablets, DRV/c/FTC/TAF swallowing tablets</td>
<td>12-17 years</td>
<td>Q2 2017</td>
</tr>
<tr>
<td>GS-US-292-1515 (NCT02276612)</td>
<td>II/III</td>
<td>EVG/c/FTC/TAF</td>
<td>12-17 years</td>
<td>Q3 2017</td>
</tr>
<tr>
<td>GS-US-236-0112 (NCT01721109)</td>
<td>II/III</td>
<td>EVG/c/FTC/TDF</td>
<td>12-17 years</td>
<td>Q3 2017</td>
</tr>
<tr>
<td>IMPAACT P1093 (NCT01302847)</td>
<td>I/II</td>
<td>DTG film-coated tablets, DTG granules for suspension</td>
<td>Up to 17 years</td>
<td>Q2 2018</td>
</tr>
<tr>
<td>ING114916 (NCT01536873)</td>
<td>III</td>
<td>DTG 50 mg (expanded access)</td>
<td>&gt; 12 years</td>
<td>Q3 2018</td>
</tr>
<tr>
<td>SMILE (PENTA 17) (NCT02383108)</td>
<td>II/III</td>
<td>EVG + DRV/r</td>
<td>6-17 years</td>
<td>Q3 2018</td>
</tr>
<tr>
<td>GS-US-380-1474 (NCT02881320)</td>
<td>II/III</td>
<td>Bictegravir/FTC/TAF</td>
<td>6-17 years</td>
<td>Q4 2018</td>
</tr>
<tr>
<td>ODYSSEY (PENTA 20) (NCT02259127)</td>
<td>II/III</td>
<td>DTG</td>
<td>6-18 years</td>
<td>Q2 2019</td>
</tr>
<tr>
<td>GS-US-311-1269 (NCT02285114)</td>
<td>II/III</td>
<td>TAF</td>
<td>6-17 years</td>
<td>Q1 2020</td>
</tr>
<tr>
<td>GS-US-216-0128 (NCT02016924)</td>
<td>II/III</td>
<td>ATV/c, DRV/c</td>
<td>3m-17 years</td>
<td>Q4 2020</td>
</tr>
<tr>
<td>GS-US-292-0106 (NCT01854775)</td>
<td>II/III</td>
<td>EVG/c/TAF/FTC</td>
<td>6-17 years</td>
<td>Q4 2021</td>
</tr>
<tr>
<td>IMPAACT 2006*</td>
<td>II</td>
<td>DTG</td>
<td>1m – 3Y</td>
<td>In development</td>
</tr>
</tbody>
</table>

*www.impaaactnetwork.org/studies
Almost unbreakable – 600 000 people on first-line DTG, no resistance (well one case, no second, third-line)

DTG slightly cheaper than EFV, TAF much cheaper than TDF – generics: immediate 20% price reduction, CHAI ?closer to 50%

Possibility of harmony for >12 years (and possibly below)

Move second-line patients BACK to 1st line
ADVANCE

Number = 1110*
≥12 years, ≥40 kg

- Non inferiority of 2 new combinations to current treatment
- Open label, randomised, single site study over 48 weeks
- * n=1110, with 90-120 in age group 12-18 years
Reformulation of existing ARV’s


Figure 5. Schematic representation of a lipid nanoparticle with combined antiretroviral drugs. The lipophilic
Safety issues with PIs

**LPV/r**
- GI upset
- Lipids
- Hepatitis
- Dysglycaemia

**ATV/r**
- Jaundice
- Lipids (low potential)
- Renal stones
- Hepatitis

**DRV/r**
- Rash
- GI upset
- Hepatitis
How do we make PIs safer?

• New molecules
• Prodrugs of current PIs
  – Improve bioavailability
  – Reduce side effects
• New formulations of existing PIs
• Different pharmacokinetic boosters
• Use existing PIs in a different ways
  – Lower doses
  – Different combinations e.g. nuke sparing
Some new approaches...

- Dual (and mono) therapy!
- Injectables
- And new classes, immunoglobulins
Reduced drug regimens in suppressed and naive patients. Simplicity 2.0

2015

DTG + 3TC (Paddle)

2016

CABT LA + RPV LA (LATTE-2)

2017

DTG + RPV (SWORD)

DTG + 3TC (GEMINI & TANGO)
(Actg 5353 & ASPIRE)
(Lamidol)

...'

CABT LA + RPV LA
(FLAIR & ATLAS)

ISTI + NNRTI
ISTI + 3TC

Courtesy Jose Arribas
Uptake of contraceptive implants in SSA

FIGURE 1. Contraceptive Method Mix Among New Family Planning Users in Program Areas in Chad and DRC, June 2011 to November 2015

- Rattan J et al., Global Health: Sci Prac 2016; 4: Suppl 2
Cabotegravir LA and Rilpivirine LA Nanosuspensions

- Drug nanocrystal suspended in liquid = nanosuspension
- Nanomilled to increase surface area and drug dissolution rate
- Allows ~100% drug loading vs. matrix approaches for lower inj. volumes

**GSK744 200mg/mL**

<table>
<thead>
<tr>
<th>Component</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSK1265744 (d50 ~200 nm)</td>
<td>Active</td>
</tr>
<tr>
<td>Mannitol</td>
<td>Tonicity agent</td>
</tr>
<tr>
<td>Surfactant System</td>
<td>Wetting/Stabilizer</td>
</tr>
<tr>
<td>Water for Injection</td>
<td>Solvent</td>
</tr>
</tbody>
</table>

**TMC278 300mg/mL**

<table>
<thead>
<tr>
<th>Component</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMC278 (d50 ~200 nm)</td>
<td>Active</td>
</tr>
<tr>
<td>Glucose</td>
<td>Tonicity agent</td>
</tr>
<tr>
<td>Surfactant System</td>
<td>Wetting/Stabilizer</td>
</tr>
<tr>
<td>Water for Injection</td>
<td>Solvent</td>
</tr>
</tbody>
</table>

And nanoparticles....
First-in-Class Capsid Inhibitor GS-CA1
GS-CA1 Inhibits Multiple Steps in HIV Replication Cycle

Dissect replication cycle for points of GS-CA1 action:

- Full single round of replication
  - EC₅₀ = 85 pM

Infectious virus production

- Producer cell
  - Gag
  - Gag-Pol

- Capsid Core Assembly

- Maturation

- Target cell infection

- Reverse Transcription

- Capsid Core Disassembly

- Pre-integration complex

- Nuclear Translocation

- Integration

Tse et al. CROI 2017 - abstract 38
So, lifetime treatment means...

- Less and less tolerance for “nuisance” side effects
- Far less focus on the initiation period, sickness
- Interest in contribution of ARVs & HIV to other non-communicable disease risk factors
- Focus on costs – especially of drugs
- Focus on longer-acting injectables, implantables
- Interest in “cure”
- Unacceptable to have “lesser” drugs in lower-income countries – complex!
- Harmonisation between paeds and adults
Thank you
USAID, UNITAID, WHO, HIV i-Base, CHAI, Mylan, ICAP, MPP, Andrew Hill, Anton Pozniak, Marta Boffito, Michelle Moorhouse
Save the Date

SOUTHERN AFRICAN HIV CLINICIANS SOCIETY CONFERENCE 2018

JOHANNESBURG, SOUTH AFRICA | 24 - 27 OCTOBER 2018

- Current and thought-provoking academic presentations
- Fascinating ethics sessions
- Practical sessions including case studies and skills-building workshops
- CPD accredited

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