Exploring First-line ART Strategies: Dolutegravir

Michelle Moorhouse
Mar 2018
First-line ART Strategies Roadshow
Disclosures

• Speaker fees and honoraria from Gilead Sciences, AbbVie, Cipla, Mylan and Janssen, and has received conference sponsorship from BD, Gilead, Janssen, Merck, Cipla and Mylan.

• Part of ART optimisation collaborations

• Funding from USAID, Unitaid, SAMRC and study drug donations from ViiV Healthcare and Gilead Sciences for ART optimisation studies
The evolving HIV treatment paradigm

- HIV-1 discovered
- ZDV monotherapy
- ZDV/3TC
- Triple-Drug Therapy
- Single-Tablet Regimens
- The Integrase Era
- Long Acting Injectable?

3TC=lamivudine; ZDV=zidovudine


Joe Eron
ART trials

114 studies through 2010, up to 3 years of f/u: ITT analyses

Virologic responses

Safety and tolerability

Lee et al. PLoS One 2014
The drugs rock

- TDF
- XTC
- Efavirenz

Failure

- AZT
- 3TC
- PI/r (LPV or ATV)

Failure

XTC, other nukes

- Darunavir
- Dolutegravir
- Etravirine
But there’s room for improvement

Some day drugs will be perfect
If we try
Some day drugs will be perfect
And no one will ever die

Some day risk will be zero
My, oh my
Some day pills will be magic
And they’ll taste of apple pie
First-line....

<table>
<thead>
<tr>
<th>Desirable Property</th>
<th>EFV/TDF/FTC</th>
</tr>
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<tbody>
<tr>
<td>High resistance barrier</td>
<td>No</td>
</tr>
<tr>
<td>Well tolerated</td>
<td>Not initially</td>
</tr>
<tr>
<td>No lab tox monitoring</td>
<td>TDF creat</td>
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<tr>
<td>Safe in pregnancy</td>
<td>Yes</td>
</tr>
<tr>
<td>Low pill burden</td>
<td>Yes FDC</td>
</tr>
<tr>
<td>Once a day</td>
<td>Yes</td>
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<tr>
<td>Use with TB (rifampicin)</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**Toxicity driver**
- Pill size
- Low genetic barrier
- Cost
Efavirenz’s side effects...

- Neuro-psychiatric
  - Ann Intern Med. 2005;143:714

- Suicide

- Metabolic
  - PLoSMed 2004;1:e19
  - JAIDS 2012;60:33
  - Lancet Infect Dis 2012;12:111
  - Clin Infect Dis 2006;42:273
  - Lancet 2009; 374: 796
  - AIDS 2014;28(10):145
  - JAIDS 2011;57:2841
  - Karamchand Medicine 2016

- Bone mineral density
  - Dave PLoS ONE 10(12): e0144286.

- DILI
  - Sonderup AIDS 2016

- Late encephalopathy
  - Variava JAIDS 2017
Has the time come to abandon efavirenz for first-line antiretroviral therapy?

Francois Raffi¹*, Anton L. Pozniak² and Mark A. Wainberg³

Increasing primary resistance

Toxicity issues

Newer regimens more effective

High income countries no longer recommend EFV in first-line
Comparison of current international guidelines for ART-naive

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<tbody>
<tr>
<td>DTG/3TC/ABC*</td>
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<tr>
<td>DTG + FTC/TDF</td>
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<tr>
<td>EVG/COBI/FTC/TDF†</td>
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<tr>
<td>EVG/COBI/FTC/TAF‡</td>
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<tr>
<td>RAL + FTC/TDF</td>
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<tr>
<td>ATV/RTV + FTC/TDF</td>
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<tr>
<td>DRV/RTV + FTC/TDF</td>
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<tr>
<td>Efavirenz/FTC/TDF</td>
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</tr>
<tr>
<td>Raltegravir/FTC/TDF§</td>
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</tbody>
</table>

*Only if HLA-B*5701 negative. †Only if CrCl ≥ 70 mL/min. ‡Only if CrCl ≥ 30 mL/min. §Only if baseline HIV-1 RNA < 100,000 copies/mL and CD4+ cell count > 200 cells/mm³.

Recommended | Alternative | Not included

3. BHIVA Guidelines. 2015.

Slide credit: clinicaloptions.com
“The integrase inhibitor era”

Shift To Integrase Inhibitor-based Therapy
Initial Antiretroviral Therapy

ART regimen type by year of initiation

1,773 patients initiating ART between 1996 and 2014 in the UCHCC, follow-up through 2015

bPI = LPV/r, DRV/r or ATV/r therapy
Other = includes unboosted PI and other bPI combinations

Thanks Joe Eron
Even LMICs: 40% shifting to DTG (only 5% already completed)

Estimated number of PLHIV on DTG (as Dec 2017):
- Brazil: 80,000
- Botswana: 52,000
- Kenya: 2,000
- Nigeria: >350
- Uganda: >200

High income countries: > 300,000

Courtesy of M. Vitoria
We know DTG works in ARV-naives

- Randomised, non-inferiority phase 3 studies
- Primary endpoint: HIV-1 RNA < 50 copies/mL at week 48

**SPRING-2**
(active controlled)

- ART-naive pts
- VL ≥ 1000 c/mL
- (N = 822)

- DTG 50 mg QD + 2 NRTIs*
  - (n = 411)

- RAL 400 mg BID + 2 NRTIs*
  - (n = 411)

**SINGLE**
(placebo controlled)

- ART-naive pts
- VL ≥ 1000 c/mL
- HLA-B*5701 neg
- CrCl > 50 mL/min
- (N = 833)

- DTG 50 mg QD + ABC/3TC QD
  - (n = 414)

- EFV/TDF/FTC QD
  - (n = 419)

**FLAMINGO**
(open label)

- ART-naive pts
- VL ≥ 1000 c/mL
- (N = 484)

- DTG 50 mg QD + 2 NRTIs*
  - (n = 242)

- DRV/RTV 800/100 mg QD + 2 NRTIs*
  - (n = 242)

*Investigator-selected NRTI backbone: either TDF/FTC or ABC/3TC.
SINGLE study: DTG vs. EFV

Better tolerated than EFV (but more insomnia)

Proportion of participants with HIV-1 RNA <50 c/mL

Week

Proportion of patients (%)

Baseline

DTG + ABC/3TC QD (n=414)

EFV/TDF/FTC QD (n=419)

Difference in response

Week 96: 8.0% (95% CI, 2.3% to 13.8%); p=0.006

Week 114: 8.3% (95% CI, 2.0% to 14.6%); p=0.010

Walmsley et al. J Acquir Immune Defic Syndr 2015
SINGLE study: safety

Discontinuations: DTG+ABC/3TC 2% vs. EFV/TDF/FTC 10%
And they do well in the real (US) world!

In CNICS cohort integrase inhibitor use was strongly associated with HIV RNA suppression
DTG in the REAL real world...

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>

ABC, abacavir; CI, confidence interval.

Hoffmann et al. HIV Medicine 2017; Libre et al. CROI 2017 abstract #615;
Hsu et al. CROI 2017 abstract #664
DTG in the REAL real world...

Dolutegravir: discontinuation due to AE
Germany (2 cohorts), 1950 INSTI-based therapies

Intolerance of dolutegravir-containing combination antiretroviral therapy regimens in real-life clinical practice

Mark G.J. de Boer\textsuperscript{a}, Guido E.L. van den Berk\textsuperscript{b}, Natasja van Holten\textsuperscript{a}, Josephine E. Oryszcyn\textsuperscript{b}, Willemien Dorama\textsuperscript{a}, Daoud ait Moha\textsuperscript{b} and Kees Brinkman\textsuperscript{b}

Log rank test, $P < 0.0001$

Neuropsychiatric AES
- Female, vs. male gender: 2.64, 1.23–5.65, 0.01
- Older age ($> 60$ years), vs. younger age: 2.86, 1.42–5.77, 0.003
- ABC with DTG initiated, vs. no ABC: 2.42, 1.38–4.24, 0.002
- DTG start in 2016, vs. in 2014/2015: 11.36, 4.31–29.41, $< 0.0001$

ABC, abacavir; CI, confidence interval.

Hoffmann et al. HIV Medicine 2017; Libre et al. CROI 2017 abstract #615; Hsu et al. CROI 2017 abstract #664
From CROI: Risk factors for neuropsychiatric events

Table 1: Adjusted Relative Hazards (RH) for the covariables of interest, using the Cox model.

<table>
<thead>
<tr>
<th>Risk factors for NPAEs leading to DTG discontinuation</th>
<th>RH</th>
<th>95 % CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, versus male gender</td>
<td>2.31</td>
<td>1.12-4.74</td>
<td>0.03</td>
</tr>
<tr>
<td>Older age (&gt; 60 years), versus younger age</td>
<td>2.14</td>
<td>1.10-4.18</td>
<td>0.025</td>
</tr>
<tr>
<td>Depressive disorders, versus no</td>
<td>1.00</td>
<td>0.54-1.88</td>
<td>0.952</td>
</tr>
<tr>
<td>Other neuropsychiatric diagnoses, versus no</td>
<td>0.93</td>
<td>0.29-3.00</td>
<td>0.896</td>
</tr>
</tbody>
</table>

Figure 3. Reasons (%) for discontinuing DTG, n=54 (mean of 2.9 symptoms/NPAEs were reported)
Case report: INSTI resistance in acute HIV treated with DTG + FTC/TDF

- 45-yr-old man, no PMH, presented with *P jirovecii* and new acute HIV diagnosis
- Initiated DTG + FTC/TDF and discharged; readmitted to ICU several days later for worsened hypoxia
- HIV-1 RNA increased after readmission despite med adherence (including DOT in hospital) and no concurrent divalent cation use
  - DRV/r added, HIV-1 RNA decreased
  - Pneumonia improved and pt discharged
- HIV-1 RNA remains suppressed; DRV/r switched to RPV for diffuse erythroderma
- Rapid INSTI emergence by deep seq: eg, Q148K population increased from 0.0015% at time point 1 to 20.9% at time point 3


Slide credit: clinicaloptions.com
Preferred option in most guidelines, but not WHO (yet)

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>NRTI Backbone</th>
<th>NNRTI</th>
<th>InSTI</th>
<th>PI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TDF/XTC</td>
<td>TAF/XTC</td>
<td>ABC/3TC</td>
<td>AZT/3TC</td>
</tr>
<tr>
<td>IAS (2016)</td>
<td>Preferred</td>
<td>Preferred</td>
<td>Preferred</td>
<td>Preferred</td>
</tr>
<tr>
<td>DHHS (2017)</td>
<td>Preferred</td>
<td>Preferred</td>
<td>Preferred</td>
<td>Preferred</td>
</tr>
<tr>
<td>EACS (2017)</td>
<td>Preferred</td>
<td>Preferred</td>
<td>Preferred</td>
<td>Preferred</td>
</tr>
<tr>
<td>WHO (2016)</td>
<td>Preferred</td>
<td>Preferred</td>
<td>Preferred</td>
<td>Preferred</td>
</tr>
</tbody>
</table>

- **Preferred**
- **Alternative**
- **Not recommended/special situations**

Courtesy of M. Vitoria; updated M. Moorhouse
Why aren’t these drugs used?

RCTs don’t address real world issues

- Women, children and LMICs under-represented in pivotal studies
- Many drugs are not registered and no co-formulations are available
- Limited data on use in TB (almost all new drugs)
- Limited data on use in pregnancy (almost all new drugs)
- Costs: abacavir, all integrase inhibitors – hope for dolutegravir
Real world patients are under-represented

**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
TB: DTG and rifampicin

DTG 50 mg 12 hourly + rif

DTG 50 mg daily

$AUC_{0-24}$ DTG 50 mg/d  32.1

DTG 50 mg 12 hourly + rifampicin  42.6
INSPIRING: Phase 3b study design

Inclusion criteria
- HIV-1 RNA ≥ 1000 copies/mL and CD4+ ≥ 50 cells/mm³
- Pulmonary, pleural, or lymph node tuberculosis with RIF-sensitive MTB confirmed by culture or GeneXpert
- RIF-containing TB treatment started up to a maximum of 8 weeks before randomisation and no later than the screening date

Primary endpoint
- Proportion of DTG subjects with plasma HIV-1 RNA <50 copies/mL at Week 48 using the modified Snapshot algorithm in the ITT-E population

Virologic and PK results through week 24

Proportion of participants with HIV-1 RNA <50 copies/mL, % (95% CI)

**Pharmacokinetic data**

**Pre-dose concentration: DTG 50 mg BID with RIF**

<table>
<thead>
<tr>
<th>Time</th>
<th>n</th>
<th>DTG Conc (ng/mL)</th>
<th>Geomean (90%CI)</th>
<th>%CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 8</td>
<td>41</td>
<td>852</td>
<td>(208-2340)</td>
<td>118</td>
</tr>
<tr>
<td>Week 24</td>
<td>22</td>
<td>942</td>
<td>(19-3380)</td>
<td>276</td>
</tr>
</tbody>
</table>

**Pre-dose concentration: DTG 50 mg QD without RIF (post-TB treatment phase)**

<table>
<thead>
<tr>
<th>Time</th>
<th>n</th>
<th>DTG Conc (ng/mL)</th>
<th>Geomean (90%CI)</th>
<th>%CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 36</td>
<td>16</td>
<td>1143</td>
<td>(80-4370)</td>
<td>151</td>
</tr>
<tr>
<td>Week 48</td>
<td>12</td>
<td>591</td>
<td>(19-3310)</td>
<td>359</td>
</tr>
</tbody>
</table>

INSPIRING DTG $C_{\text{tau}}$ when administered twice daily with RIF were similar to DTG 50 mg once daily without RIF and to previously reported data for DTG 50 mg once daily in Phase 2/3 HIV trials.

Pregnancy: Birth outcomes of first-line DTG vs EFV (Tsepmo)

Prospective cohort study in HIV-infected women in Botswana initiating ART with EFV/FTC/TDF vs DTG/FTC/TDF while pregnant (N = 5438)

<table>
<thead>
<tr>
<th>Adverse Birth Outcomes, n (%)</th>
<th>DTG (n = 845)</th>
<th>EFV (n = 4593)</th>
<th>aRR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Severe</td>
<td>291 (34.4)</td>
<td>1606 (35.0)</td>
<td>1.0 (0.9-1.1)</td>
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<tr>
<td></td>
<td>92 (10.9)</td>
<td>519 (11.3)</td>
<td>1.0 (0.8-1.2)</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>18 (2.1)</td>
<td>105 (2.3)</td>
<td>0.9 (0.6-1.5)</td>
</tr>
<tr>
<td>Neonatal death (&lt; 28 days)</td>
<td>11 (1.3)</td>
<td>60 (1.3)</td>
<td>1.0 (0.5-1.9)</td>
</tr>
<tr>
<td>Preterm birth (&lt; 37 wks)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>▪ Very preterm (&lt; 32 wks)</td>
<td>149 (17.8)</td>
<td>844 (18.5)</td>
<td>1.0 (0.8-1.1)</td>
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<tr>
<td></td>
<td>35 (4.2)</td>
<td>160 (3.5)</td>
<td>1.2 (0.8-1.7)</td>
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<tr>
<td>SGA (&lt; 10th percentile weight)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Very SGA (&lt; 3rd percentile weight)</td>
<td>156 (18.7)</td>
<td>838 (18.5)</td>
<td>1.0 (0.9-1.2)</td>
</tr>
<tr>
<td></td>
<td>51 (6.1)</td>
<td>302 (6.7)</td>
<td>0.9 (0.7-1.2)</td>
</tr>
</tbody>
</table>

*For DTG vs EFV; adjusted for maternal age, education, gravida.

Few first-trimester ART exposures (DTG, n = 116; EFV, n = 396); most second/third trimester

Only 1 major congenital abnormality observed (skeletal dysplasia in EFV-exposed group)

ABO risks similar when initiating first-line DTG vs EFV in pregnancy
CLINICAL UPDATE

Cutting the cost of South African antiretroviral therapy using newer, safer drugs

W D F Venter,1 FCP (SA), MMed; B Kaiser,2 MPH, PharmD, BCPS; Y Pillay,3 PhD; F Conradie,4 MB Bch; G B Gomez,5 PhD; P Clayden,6 M Matsolo;7 C Amole,8 BA; L Rutter,7 BA; F Abdullah,9 MB ChB, FCPHM, BSc Hons (Epi); E J Abrams,10 MD; C P Casas,11 MSc; M Barnhart,12 MD, MPH; A Pillay,13 PhD; A Pozniak,14 M M Moorhouse,1 MB Bch; M Chersich,1 MB Bch, PhD; C

1Wits Reproductive Health and HIV Institute, University of i
2Formerly UNITAID, Geneva, Switzerland
3HIV/AIDS, TB and Malaria, Child and Women's Health i

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).
Ceiling price agreement was recently announced

- This ceiling price agreement could yield billions of rand in savings through TLD rollout and enable widespread access to a clinically superior regimen
- The TLD agreement lasts four years: 01 April 2018 – 31 March 2022
But what about second-line?

TDF + XTC + Efavirenz

AZT + 3TC + PI/r (LPV or ATV)

Cost and toxicity

Darunavir, Raltegravir, Etravirine
DAWNING: Study design

Key eligibility criteria:
- on first-line 2 NRTIs + NNRTI regimen for ≥ 6 months, failing virologically (HIV-1 RNA ≥ 400 copies/mL on 2 occasions); no primary viral resistance to PIs or InSTIs

Stratification:
- by HIV-1 RNA (≤ or >100,000 copies/mL), number of fully active NRTIs in the investigator-selected study background regimen (2 or < 2)

Primary endpoint:
- proportion with HIV-1 RNA < 50 copies/mL at Week 48 using the FDA snapshot algorithm (12% noninferiority margin)

FDA, US Food and Drug Administration; INSTI, integrase strand transfer inhibitor.

Aboud et al. IAS 2017; Paris, France. Slides TUAB0105LB.
Snapshot outcomes at Week 24: ITT-E and PP Populations

- DTG + 2 NRTIs is **superior** to LPV/r + 2 NRTIs with respect to snapshot in the ITT-E (≤ 50 copies/mL) at Week 24, *P < 0.001*

  - CI, confidence interval; ITT-E, intent-to-treat exposed; PP, per protocol.

Aboud et al. IAS 2017; Paris, France. Slides TUAB0105LB.
Switching from a boosted protease inhibitor (PI/r) based regimen to a dolutegravir (DTG) regimen in virologically suppressed patients with high cardiovascular risk (Framingham score > 10% or age > 50 years) is non-inferior and decreases lipids: The NEAT 022 study

J.M. Gatell¹, L. Assoumou², G. Moyle³, L. Waters⁴, E. Martinez⁵, H.-J. Stellbrink⁶, G. Guaraldi⁷, S. de Wit⁸, F. Raffi⁹, A. Pozniak¹⁰ on behalf of NEAT022 Study Group
Results: Co-primary efficacy endpoint

ITT population

Difference (95%CI)
-2.1% (-6.6 to 2.4)

Non-inferiority margin -10%

Neat id
The European treatment network for HIV, hepatitis and global infectious diseases

ITAT22/SSAT060 week 48 data
Reduced drug regimens in ARV-naïve patients?
# Previous studies of first-line dual-therapy ART: Selected data

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Regimen</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>PADDLE&lt;sup&gt;[1]&lt;/sup&gt;</td>
<td>20</td>
<td>DTG + 3TC ARV-naives</td>
<td>18/20 pts achieved virologic suppression; n = 1 experienced PDVF (BL HIV-1 RNA &gt; 100,000 copies/mL); resuppressed HIV-1 RNA without ART change by discontinuation visit</td>
</tr>
<tr>
<td>ACTG 5353&lt;sup&gt;[2]&lt;/sup&gt;</td>
<td>120</td>
<td>DTG + 3TC ARV-naives</td>
<td>108/120 patients achieved virologic suppression at week 24; n = 3 experienced PDVF (all 3 had sub-therapeutic DTG levels)</td>
</tr>
<tr>
<td>ANRS 167 LAMIDOL&lt;sup&gt;[3]&lt;/sup&gt;</td>
<td>110</td>
<td>DTG + 3TC (Switch study)</td>
<td>97% (101/104) pts maintained virologic suppression through 40 weeks of dual therapy (study Week 48)</td>
</tr>
<tr>
<td>SWORD 1,2&lt;sup&gt;[4]&lt;/sup&gt;</td>
<td>1024</td>
<td>DTG + RPV versus continuing (Switch)</td>
<td>95% of pts in both arms maintained virologic suppression through 48 weeks of therapy (study Week 52)</td>
</tr>
</tbody>
</table>

Dolutegravir monotherapy in ART-naive

- N = 9 pts who refused NRTIs and initiated DTG monotherapy
  - All pts had baseline HIV-1 RNA < 100,000 copies/mL
  - No baseline NRTI, NNRTI, PI, or INSTI resistance

<table>
<thead>
<tr>
<th>Pt</th>
<th>HIV-1 RNA, copies/mL</th>
<th>CD4+ Cell Count, cells/mm³</th>
<th>Mos on DTG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>After 4 Wks’ DTG</td>
<td>At Last Visit</td>
</tr>
<tr>
<td>1</td>
<td>20,400</td>
<td>Undetectable</td>
<td>Undetectable</td>
</tr>
<tr>
<td>2</td>
<td>18,400</td>
<td>Undetectable</td>
<td>&lt; 20</td>
</tr>
<tr>
<td>3</td>
<td>90,500</td>
<td>31</td>
<td>Undetectable</td>
</tr>
<tr>
<td>4</td>
<td>39,000</td>
<td>35</td>
<td>Undetectable</td>
</tr>
<tr>
<td>5</td>
<td>43,300</td>
<td>&lt; 20</td>
<td>Undetectable</td>
</tr>
<tr>
<td>6</td>
<td>17,500</td>
<td>45</td>
<td>&lt; 20</td>
</tr>
<tr>
<td>7</td>
<td>18,200</td>
<td>&lt; 20</td>
<td>Undetectable</td>
</tr>
<tr>
<td>8</td>
<td>16,900</td>
<td>Undetectable</td>
<td>Undetectable</td>
</tr>
<tr>
<td>9</td>
<td>52,000</td>
<td>&lt; 20</td>
<td>Undetectable</td>
</tr>
</tbody>
</table>


Slide credit: clinicaloptions.com
DOMONO: Switch to DTG monotherapy in suppressed patients not sufficient

Comparison of randomised switch to DTG 50 mg QD monotherapy vs continued baseline ART in suppressed patients with no previous VF\(^1\)

- At Week 24, DTG monotherapy noninferior to continued baseline ART for maintained HIV-1 RNA < 200 copies/mL

- **Study discontinued early due to high rate of InSTI resistance mutations after 48 weeks of DTG monotherapy**\(^2\)
  - VF in 8/77 pts with DTG monotherapy vs 3/152 pts on combination ART in concurrent control group (\(P = 0.03\))
  - Of 8 monotherapy pts with VF, genotyping successful in 6; 3/6 with InSTI resistance (N155H, R263K, S230R, n = 1 each)


Slide credit: clinicaloptions.com
Reframing HIV care: putting people at the centre of antiretroviral delivery

Chris Duncombe¹, Scott Rosenblum¹, Nicholas Hellmann², Charles Holmes³, Lynne Wilkinson⁴, Marc Biot⁴, Helen Bygrave⁴, David Hoos⁵ and Geoff Garnett¹

Review

The levers of tiered care

- ART initiation/refills
- Clinical monitoring
- Adherence support
- Laboratory tests
- OI treatment
- Psychosocial support

Summary

Service intensity

Service frequency

Every 3 months

Every 6 months

Monthly

Bi-monthly

Every 2 months

Health worker cadre

Physician

Clinical Officer

Nurse

Pharmacist

Community Health Worker

Patient/peer/family

Service location

Home

HIV clinic/hospital

Primary care clinic

Other clinic

Community

Figure 1 Four levers to tailor or adapt care to people’s needs (service frequency, location, intensity and cadre).
Comparing third drugs

<table>
<thead>
<tr>
<th>Desirable Property</th>
<th>EFV</th>
<th>RPV</th>
<th>DTG</th>
</tr>
</thead>
<tbody>
<tr>
<td>High resistance barrier</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Well tolerated</td>
<td>Not initially</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>No lab tox monitoring</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Safe in pregnancy</td>
<td>Yes</td>
<td>Limited data</td>
<td>Increasing data</td>
</tr>
<tr>
<td>Low pill burden</td>
<td>FDC</td>
<td>No FDC in SA</td>
<td>No FDC yet</td>
</tr>
<tr>
<td>Once a day</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Use with TB (rifampicin)</td>
<td>Yes</td>
<td>No</td>
<td>Dose bid</td>
</tr>
</tbody>
</table>

... data

Low pill burden

FDC

No FDC in SA

No FDC yet

Dose bid
Comparative efficacy and safety of first-line ART: A systematic review and network meta-analysis

Network of eligible comparisons between treatments

Kanter S, Lancet 2016
DTG is here

Superiority to currently used ARVs
Robust with a formidable resistance barrier
Well-tolerated in RCTS
Real-world tolerability is emerging
Dual therapy?
ART alone is not enough
Acknowledgements