Exploring First-line ART Strategies: Dolutegravir

Michelle Moorhouse
Oct 2017
First-line ART Strategies Roadshow

University of the Witwatersrand
WITS RHI

SOUTHERN AFRICAN HIV CLINICIANS SOCIETY
The evolving HIV treatment paradigm

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

Timeline:
- 1983
- 1987
- 1995
- 1996
- 2006
- 2012–2013
- 2017
- 2020

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

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>
</thead>
<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>
</tr>
<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>
</tr>
<tr>
<td>Use with TB (rifampicin)</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Cost driver: Toxity

Toxicity driver: Pill size, Low genetic barrier, Cost
Efavirenz’s warts...

Neuropsychiatric

Ann Intern Med. 2005;143:714

Suicide

Ann Intern Med. 2014;161:1-10

Late encephalopathy

Variava JAIDS 2017

DILI

Sonderup AIDS 2016

Bone mineral density

Dave PLoS ONE 10(12): e0144286.

Metabolic

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
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

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>DTG/3TC/ABC*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DTG + FTC/TDF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EVG/COBI/FTC/TDF†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EVG/COBI/FTC/TAF‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAL + FTC/TDF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATV/RTV + FTC/TDF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DRV/RTV + FTC/TDF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EFV/FTC/TDF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RPV/FTC/TDF§</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</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.
“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

Courtesy of Thibaut Davy and Sonia Napraivnik

Thanks Joe Eron
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.

Clinical Care Options 2014
Raffi et al. Lancet Infect Dis 2013
Clotet et al. Lancet 2014
SINGLE study: DTG vs. EFV

Better tolerated than EFV (but more insomnia)

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

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
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...

Discontinuation due to
europsychiatric 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 (≥ 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 (≥ 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. Oryszczyn\textsuperscript{b}, Willemien Dorama\textsuperscript{a}, Daoud ait Moha\textsuperscript{b} and Kees Brinkman\textsuperscript{b}

AIDS 2016

Hoffmann et al. HIV Medicine 2017; Libre et al. CROI 2017 abstract #615; Hsu et al. CROI 2017 abstract #664
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

Preferred option in most guidelines, but not WHO

<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>ABC/3TC</td>
<td>AZT/3TC</td>
<td>EFV</td>
</tr>
<tr>
<td>IAS (2014)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DHHS (2015)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EACS (2015)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO (2015)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Preferred
- Alternative
- Not recommended/special situations

<table>
<thead>
<tr>
<th>GUIDELINES</th>
<th>Preferred first-line options</th>
<th>Alternative first-line options</th>
</tr>
</thead>
<tbody>
<tr>
<td>IAS (2014)</td>
<td>11</td>
<td>16</td>
</tr>
<tr>
<td>DHHS (2015)</td>
<td>05</td>
<td>07</td>
</tr>
<tr>
<td>EACS (2015)</td>
<td>06</td>
<td>13</td>
</tr>
<tr>
<td>WHO (2015)</td>
<td>01</td>
<td>05</td>
</tr>
</tbody>
</table>

Courtesy of M. Vitoria
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
TB: DTG and rifampicin

AUC$_{0-24}$ DTG 50 mg/d  32.1
DTG 50 mg 12 hourly + rif  42.6
Pregnancy: Birth outcomes of first-line DTG vs EFV (Tsepamo)

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>
</tr>
<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>
</tr>
<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>
</tr>
<tr>
<td></td>
<td>35 (4.2)</td>
<td>160 (3.5)</td>
<td>1.2 (0.8-1.7)</td>
</tr>
<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>51 (6.1)</td>
<td>302 (6.7)</td>
<td>0.9 (0.7-1.2)</td>
</tr>
<tr>
<td></td>
<td>156 (18.7)</td>
<td>838 (18.5)</td>
<td>1.0 (0.9-1.2)</td>
</tr>
<tr>
<td></td>
<td>306 (35.0)</td>
<td>1625 (35.0)</td>
<td></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
Costs

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 Maternal, 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).
Real world patients are underrepresented

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
But what about second-line?
[and why am I talking about it in a talk on first-line?]
**DAWNING: Study design**

Open-label randomised noninferiority phase 3b study

- **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 <5 0 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

Virologic outcomes

Treatment differences (95% CI)

- DTG + 2 NRTIs is superior to LPV/RTV + 2 NRTIs with respect to snapshot in the ITT-E (<50 c/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.
Snapshot outcomes at Week 24: ITT-E and PP Populations

- DTG + 2 NRTIs is superior to LPV/RTV + 2 NRTIs with respect to snapshot in the ITT-E (<50 c/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.
The Doodle study

Number = 470
VL < 50 copies/mL
On PI/r-based ART
≥ 12 years, ≥ 40 kg

1:1

DTG 50 mg + TDF 300 mg + FTC 200 mg

PI/r + TDF 300 mg + FTC 200 mg

<table>
<thead>
<tr>
<th>Screen</th>
<th>Enrolment</th>
<th>Visit 1/2</th>
<th>Visit 3</th>
<th>Visit 4</th>
<th>Visit 5</th>
<th>EOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day -60 to -1</td>
<td>Week 0</td>
<td>Week 4/8</td>
<td>Week 12</td>
<td>Week 24</td>
<td>Week 36</td>
<td>Week 48</td>
</tr>
</tbody>
</table>

Randomisation

Primary endpoint

NEAT 022 study?
Reduced drug regimens in ARV-naïve patients?

- DTG + 3TC (Paddle)
- DTG + RPV (SWORD)
- DTG + 3TC (GEMINI & TANGO) (ACTG 5353 & ASPIRE) (Lamidol)

2015

2016

2017

CABT LA + RPV LA (LATTE-2)

CABT LA + RPV LA (FLAIR & ATLAS)

ISTI + NNRTI

ISTI + 3TC

Courtesy J Arribas
## 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>NEAT001(^1)</td>
<td>805</td>
<td>DRV/RTV + RAL</td>
<td>Similar efficacy as DRV/RTV + FTC/TDF; poor efficacy in pts with high HIV-1 RNA, low CD4+ cell counts</td>
</tr>
<tr>
<td>GARDEL(^2)</td>
<td>426</td>
<td>LPV/RTV + 3TC</td>
<td>Similar efficacy as LPV/RTV + 2 NRTIs</td>
</tr>
<tr>
<td>PADDLE(^3)</td>
<td>20</td>
<td>DTG + 3TC</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>
</tbody>
</table>


\(^{1}\) Slide credit: clinicaloptions.com

ANDES and ACTG A5353 studies presented at IAS 2017
ANRS 167 LAMIDOL: Switch to DTG + 3TC from suppressive triple ART

Noncomparative, open-label, single-arm multicentre trial

• Primary endpoint: therapeutic success at Week 56 (ie, after 48 weeks of dual therapy)
  – Therapeutic failure: HIV-1 RNA > 50 copies/mL, interruption, LTFU, death

HIV-infected pts with HIV-1 RNA ≤ 50 copies/mL for ≥ 2 years on first-line ART; ≤ 2 ART modifications allowed, except within 6 months of study start; CD4 cell count > 200 cells/mm³ (N = 110)

*Pts with HIV-1 RNA ≤ 50 copies/mL proceeded to phase 2.
†In phase I, third agent in regimen replaced with DTG; baseline NRTI backbone maintained.

Slide credit: clinicaloptions.com
LAMIDOL interim analysis: Switch to DTG + 3TC maintains suppression

- 97% (101/104) pts maintained therapeutic success through 40 weeks of dual therapy (study Week 48)\(^1\)
  - No INSTI resistance in 3 pts with virologic failure
  - 7 pts with serious AEs, only 2 related to dual therapy
- DTG + 3TC dual therapy currently under phase 3 evaluation as both initial ART\(^2,3\) and as a switch strategy for virologically suppressed pts\(^4\)

<table>
<thead>
<tr>
<th>Therapeutic Success, n/N* (%)</th>
<th>DTG + 3TC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 0 (entry; on BL triple therapy)</td>
<td>110/110 (100)</td>
</tr>
<tr>
<td>Week 8 (end of phase I, start of phase II)</td>
<td>104/104 (100)</td>
</tr>
<tr>
<td>Week 12</td>
<td>104/104 (100)</td>
</tr>
<tr>
<td>Wk 16</td>
<td>103/104 (99)</td>
</tr>
<tr>
<td>Week 24</td>
<td>103/104 (99)</td>
</tr>
<tr>
<td>Wk 32</td>
<td>103/104 (99)</td>
</tr>
<tr>
<td>Week 40</td>
<td>102/104 (98)</td>
</tr>
<tr>
<td>Wk 48</td>
<td>101/104 (97)</td>
</tr>
</tbody>
</table>

*Pts enrolled in phase 1, N = 110; pts enrolled in phase 2, N = 104.

ACTG A5353: DTG + 3TC for ARV-naïves

- Single-arm phase 2 study\(^1\)
  
  ART-naïve pts with HIV-1 RNA ≥ 1000 and < 500 000 copies/mL; no RT, INSTI, major PI resistance mutations (N = 120)

- Baseline: 31% HIV-1 RNA > 100 000 copies/mL

<table>
<thead>
<tr>
<th>Virologic Outcome at Wk 24, n (%)</th>
<th>Baseline HIV-1 RNA, copies/mL</th>
<th>Total (N = 120)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt; 100,000 (n = 37)</td>
<td>108 (90)</td>
</tr>
<tr>
<td></td>
<td>≤ 100,000 (n = 83)</td>
<td></td>
</tr>
<tr>
<td>Success*</td>
<td>33 (89)</td>
<td>75 (90)</td>
</tr>
<tr>
<td>Nonsuccess</td>
<td>3 (8)</td>
<td>5 (4)</td>
</tr>
<tr>
<td>No data</td>
<td>1 (3)</td>
<td>7 (6)</td>
</tr>
</tbody>
</table>

  *HIV-1 RNA < 50 copies/mL.

- n = 3 with PDVF; n = 1 with emergent M184V and R263R/K mixture
  - All 3 pts had DTG levels reflective of suboptimal adherence

- GEMINI 1/2 randomised phase 3 trials of DTG + 3TC ongoing\(^2,3\)

SWORD 1, 2: Switch from suppressive ART to DTG + RPV (no previous VF)

- Randomised, open-label phase 3 trials in which virologically suppressed pts with no previous virologic failure continued with baseline ART or switched to DTG + RPV (N = 1024)[1]
  - 70% to 73% of pts receiving TDF at baseline

1 pt receiving DTG + RPV with confirmed criteria for virologic withdrawal at Week 36 had K101K/E
  - Documented nonadherence at virologic failure; resuppressed with continued DTG + RPV
  - No INSTI resistance

- AE rates generally similar between treatment arms through Week 52; numerically higher rate of withdrawal for AEs with switch: 4% vs < 1%
- For pts on TDF-containing regimens at BL (n = 102), improvements in BMD with switch[2]

---

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>1</td>
<td>20,400</td>
<td>Undetectable</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>18,400</td>
<td>Undetectable, &lt; 20</td>
<td>9</td>
</tr>
<tr>
<td>3</td>
<td>90,500</td>
<td>31</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>39,000</td>
<td>35</td>
<td>7</td>
</tr>
<tr>
<td>5</td>
<td>43,300</td>
<td>&lt; 20</td>
<td>7</td>
</tr>
<tr>
<td>6</td>
<td>17,500</td>
<td>45</td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td>18,200</td>
<td>&lt; 20</td>
<td>6</td>
</tr>
<tr>
<td>8</td>
<td>16,900</td>
<td>Undetectable</td>
<td>8</td>
</tr>
<tr>
<td>9</td>
<td>52,000</td>
<td>&lt; 20</td>
<td>6</td>
</tr>
</tbody>
</table>

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\textsuperscript{[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\textsuperscript{[2]}
  - VF in 8/77 pts with DTG monotherapy vs 3/152 pts on combination ART in concurrent control group ($P = .03$)
  - Of 8 monotherapy pts with VF, genotyping successful in 6; 3/6 with INSTI resistance (N155H, R263K, S230R, $n = 1$ each)

\textsuperscript{2} Wijting I, et al. CROI 2017. Abstract 451LB.

Slide credit: clinicaloptions.com
Review

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

The levers of tiered care

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

Summary

WHERE’S WALRY?

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>Limited 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>
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