Switching antiretroviral therapy to safer strategies based on integrase inhibitors

Dr Paddy Mallon

UCD HIV Molecular Research Group
UCD School of Medicine
paddy.mallon@ucd.ie
WE NEED SAFER DRUGS!!
Reasons to switch

- To decrease polypharmacy
- To simplify dosing (food effects) / monitoring
- To reduce potential for drug-drug interactions
- To manage / avoid adverse events
- Better safety in special circumstances - pregnancy
- To decrease cost (medications, labs, clinic visits)
Reasons NOT to switch?

• If it ain’t broke, don’t fix it
• ‘Threshold’ of toxicity / tolerability
• Can you be sure the switch will fix the problem?
• Potential to introduce new toxicities
• Will the switch be as effective?
• Virological failure (new resistance)
• Short-term gain, long-term costs – generics
Switching to InSTI as a ‘safer’ option

Raltegravir

Elvitegravir

Dolutegravir

*please note pictures do not represent actual size 😮
Switching to InSTI as a ‘safer’ option

Raltegravir

Elvitegravir

Dolutegravir

Raltegravir

Elvitegravir

Dolutegravir
Switching to raltegravir

SWITCHMRK (032/033)

N= 340 subjects per study

- Stable on LPV/r (b.i.d.) & 2 NRTIs (and no other active PI) for ≥ 3 months
- HIV RNA <50 c/mL past 3 mths
- Patients with prior virologic failure were not excluded
- No LLT past 12 weeks

Primary endpoints:
Week 12: Mean % change in lipids (Total-C, Triglycerides, non-HDL-C and LDL-C)
Week 24: Proportion with viral load <50 copies/mL by Non-completer = Failure (NC=F)

Switching to raltegravir

SWITCHMRK (032/033) study

Mean % Change in lipids from BL at Week 12

**Protocol 032**

- Fasting Cholesterol: 
  - RAL + ARTs: -13% (P<0.001)
  - LPV/r + ARTs: -15% (P<0.001)
- Non-HDL-C: 
  - RAL + ARTs: 4% (P=0.704)
  - LPV/r + ARTs: -2% (P=0.704)
- Fasting Triglycerides:
  - RAL + ARTs: 2% (P<0.001)
  - LPV/r + ARTs: 1% (P<0.001)
- Fasting LDL-C: 
  - RAL + ARTs: -41% (P<0.001)
- Fasting HDL-C: 
  - RAL + ARTs: 1% (P<0.001)

**Protocol 033**

- Fasting Cholesterol: 
  - RAL + ARTs: -12% (P<0.001)
  - LPV/r + ARTs: -15% (P<0.001)
- Non-HDL-C: 
  - RAL + ARTs: 8% (P=0.269)
  - LPV/r + ARTs: 4% (P=0.269)
- Fasting Triglycerides:
  - RAL + ARTs: 1% (P<0.001)
  - LPV/r + ARTs: 1% (P<0.001)
- Fasting LDL-C: 
  - RAL + ARTs: -43% (P<0.001)
- Fasting HDL-C: 
  - RAL + ARTs: -3% (P<0.001)

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*Median Percent Change**  **Not prespecified for test**

Mean mg/dL: Fasting Cholesterol, Non-HDL-C, Fasting Triglycerides, Fasting LDL-C, Fasting HDL-C

Switching to raltegravir

SWITCHMRK (032/033) study
Virological outcomes

<table>
<thead>
<tr>
<th>Difference (95% CI)</th>
<th>LPV/r as First Regimen</th>
<th>History of Virologic Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>−2.5 (−10.6, 5.4)</td>
<td>−15.3 (−24.9, −6.2)</td>
</tr>
<tr>
<td></td>
<td>−8.3 (−14.8, −2.1)</td>
<td>−1.0 (−6.9, 4.9)</td>
</tr>
</tbody>
</table>

% of Patients With HIV RNA <50 Copies/mL

- LPV/r First Regimen: RAL 88, LPV/r 90
- LPV/R Not First Regimen: RAL 83, LPV/r 91
- Prior Virologic Failure: RAL 77, LPV/r 92
- No Prior Virologic Failure: RAL 89, LPV/r 90

CI = confidence interval; LPV/r = lopinavir/ritonavir; RAL = raltegravir. All patients who did not complete the study were regarded as failures.

bCalculated by the method of Miettinen and Nurminen.

Switching to raltegravir

SPIRAL study
Study design – open labeled RCT

Study Population (N = 286)
Patients on current PI/r + at least 2 ARV
for ≥ 6 months
VL<50 cp/mL within 180 days

1:1 Randomization
Stratified by presence or not of lipid lowering agents

Switch to Raltegravir†
(N = 143)

Continue with boosted PI
(N = 143)

Analysis, Week 48

* Raltegravir 400mg BID (maintaining other antiretrovirals unchanged).

Martinez E et al. AIDS 2010Jul 17;24(11):1697-707
Switching to raltegravir

SPIRAL study
Virological outcomes

Free of Treatment Failure (ITT, S=F)

Free of Virologic Failure (≥ 50 cp/mL) (OT)

Outcomes not influenced by previous virological failures

Switching to raltegravir

SPIRAL study
Changes in lipids

Martinez E et al. AIDS 2010 Jul 17;24(11):1697-707
Switching to raltegravir

SPIRAL study
Changes in CVD and inflammatory biomarkers

Martinez E et al. AIDS. 2012 Nov 28;26(18):2315-26
Switching to raltegravir

Protocol 003
Double-blind, RCT

EFV QD vs RAL BID
96 week followup

83% RAL vs 84% EFV with HIVRNA<50c/ml @ wk96

TABLE 4. Summary of Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Raltegravir, 400 mg Twice a Day, (N = 160) n (%)</th>
<th>Efavirenz, 600 mg Every Day, (N = 38) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>One or more clinical adverse events</td>
<td>146 (91.3)</td>
<td>35 (92.1)</td>
</tr>
<tr>
<td>Serious clinical adverse events</td>
<td>16 (10.0)</td>
<td>3 (7.9)</td>
</tr>
<tr>
<td>Discontinued due to clinical adverse event</td>
<td>2 (1.3)</td>
<td>1 (2.6)</td>
</tr>
<tr>
<td><em><em>Drug-related</em> clinical adverse events</em>*</td>
<td>146 (91.3)</td>
<td>35 (92.1)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>11 (6.9)</td>
<td>4 (10.5)</td>
</tr>
<tr>
<td>Nausea</td>
<td>20 (12.5)</td>
<td>5 (13.2)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4 (2.5)</td>
<td>3 (7.9)</td>
</tr>
<tr>
<td>Flatulence</td>
<td>9 (5.6)</td>
<td>1 (2.6)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>14 (8.8)</td>
<td>11 (28.9)</td>
</tr>
<tr>
<td>Headache</td>
<td>14 (8.8)</td>
<td>9 (23.7)</td>
</tr>
<tr>
<td>Abnormal dreams</td>
<td>10 (6.3)</td>
<td>7 (18.4)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>13 (8.1)</td>
<td>4 (10.5)</td>
</tr>
<tr>
<td>Nightmares</td>
<td>0 (0.0)</td>
<td>4 (10.5)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>8 (5.0)</td>
<td>2 (5.3)</td>
</tr>
<tr>
<td>Malaise</td>
<td>2 (1.3)</td>
<td>3 (7.9)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>2 (1.3)</td>
<td>2 (5.3)</td>
</tr>
<tr>
<td>Lethargy</td>
<td>2 (1.3)</td>
<td>2 (5.3)</td>
</tr>
<tr>
<td>Disturbance in attention</td>
<td>1 (0.6)</td>
<td>2 (5.3)</td>
</tr>
<tr>
<td>One or more laboratory adverse events</td>
<td>38 (23.8)</td>
<td>11 (28.9)</td>
</tr>
<tr>
<td>Discontinued due to laboratory adverse event</td>
<td>1 (0.6)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td><em><em>Drug-related</em> laboratory adverse events</em>*</td>
<td>19 (11.9)</td>
<td>3 (7.9)</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>7 (4.4)</td>
<td>2 (5.3)</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>6 (3.8)</td>
<td>2 (5.3)</td>
</tr>
</tbody>
</table>

Markowitz M et al. JAIDS 2009; 52;:350-356
## Switching to raltegravir

### SPIRAL study

Tolerability outcomes

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>RALTEGRAVIR</th>
<th>PI/r</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with AE leading to study drug discontinuation</td>
<td>N = 142 N (%)</td>
<td>N = 140 N (%)</td>
</tr>
<tr>
<td>Neuropsychiatric</td>
<td>3 (2)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Patients with Serious Adverse Event</td>
<td>6 (4)</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Neuropsychiatric</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Digestive</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Respiratory</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Martinez E et al. AIDS 2010 Jul 17;24(11):1697-707
Switching to InSTI as a ‘safer’ option

- **Raltegravir**
  - 200mg

- **Elvitegravir**
  - Stribid
  - Genvoya

- **Dolutegravir**
  - Dolutegravir
  - Triumeq
Switching to Genvoya

Study 109: virologically suppressed adults switching from TDF-based regimen to Genvoya
96 week, randomised, open-label, active-controlled Phase III study

**Inclusion criteria:**
- HIV-suppressed adults on ART (E/C/F/TDF, EFV/FTC/TDF, or boosted ATV + FTC/TDF)
- All patients were virologically suppressed* and had been on a TDF-based regimen for ≥ 96 weeks
  - CrCl >50 mL/min

**Primary endpoint:**
- Proportion with HIV-1 RNA <50 copies/mL at Week 48

*Virological suppression: plasma HIV-1 RNA <50 copies/mL

E, elvitegravir; C, cobicistat; FTC, emtricitabine; TDF, tenofovir disoproxil fumarate; EFV, efavirenz; ATV, atazanavir; OD, once daily; CrCl, creatinine clearance

Switching to Genvoya

Study 109
Primary endpoint - switch to Genvoya non-inferior at week 48
Better virological success rates versus remaining on TDF-based regimens

TDF, tenofovir disoproxil fumarate

Switching to Genvoya

Study 109
Statistically significantly lower quantitative proteinuria at week 48 versus remaining on TDF-containing regimens (all \( P<0.001 \))

Switching PI to Elvitegravir/c

STRATEGY PI – multicentre, randomised, open-label, 96 week study

PI + RTV + FTC/TDF

- HIV-1 RNA <50 c/mL for ≥6 months
- ≤ 2 prior ARV regimens
- No resistance to FTC or TDF
- eGFR_{CG} ≥70 mL/min

n = 293

2:1

E/C/F/TDF (Stribild®)

PI + RTV + FTC/TDF

n = 140

Week 48

Week 96

Primary endpoint: HIV-1 RNA <50 c/mL at Week 48 by Snapshot (noninferiority margin of 12%). If noninferiority is established, then superiority will be tested.

Secondary endpoint: Safety and tolerability at Week 48 & 96

Other endpoints: Patient reported outcomes*

*HIV Symptom Index and HIV Treatment Satisfaction questionnaires

E/C/F/TDF: single-tablet regimen elvitegravir 150mg, cobicistat 150mg, emtricitabine 200mg, tenofovir DF 300mg; Stribild®

PI + RTV + FTC/TDF: ritonavir-boosted protease inhibitor and emtricitabine/tenofovir DF

Study GS-US-236-0115 is registered with ClinicalTrials.gov, number NCT01475838.

Switching PI to Elvitegravir/c

STRATEGY PI – primary endpoint: HIVRNA <50 cps/ml

Virologic Success W48: 94% for E/C/F/TDF (n=290) vs 87% for PI + RTV + FTC/TDF (n=139)

95% CI for Difference

Favors PI + RTV + FTC/TDF

Favors E/C/F/TDF

Prespecified sequential testing
Statistical superiority
(p = 0.025)

Full analysis set excluded subjects with protocol-prohibited mutations on historical genotype and those not on PI at randomization.

Switching PI to Elvitegravir/c

STRATEGY PI – change in fasting lipids

P values for all comparisons between treatment groups using ANOVA or Wilcoxon Rank Sum were not significant except for TG (p <0.001)

Changes from baseline in total cholesterol/HDL ratios were not statistically significant.

Decreases from baseline in triglycerides at Week 48 after switching to E/C/F/TDF

Switching PI to Elvitegravir/c

STRATEGY PI – change in fasting lipids with switch from LPVr

<table>
<thead>
<tr>
<th></th>
<th>TC</th>
<th>LDL</th>
<th>TG</th>
<th>HDL</th>
</tr>
</thead>
<tbody>
<tr>
<td>E/C/F/TDF (n =49)</td>
<td>-25</td>
<td>-13</td>
<td>-9</td>
<td>-2</td>
</tr>
<tr>
<td>LPV/RTV+FTC/TDF (n =23)</td>
<td>-1</td>
<td>-9</td>
<td>-46</td>
<td>5</td>
</tr>
</tbody>
</table>

P values for all comparisons between treatment groups using Wilcoxon Rank Sum test

P =0.002
P =0.16
P =0.003
P =0.016

Changes from baseline in total cholesterol/HDL ratios were not statistically significant.

Decreases from baseline in TC, TGs, and HDL at Week 48 after switching from LPV/RTV to E/C/F/TDF

Subjects who switched to E/C/F/TDF from PI + RTV + FTC/TDF had

- Lower rates of diarrhea and bloating at Week 48 compared to baseline
- Higher treatment satisfaction scores at Week 24 (mean: 23 vs. 15, p <0.001)^

^ HIV Treatment Satisfaction questionnaire, score range: -30 to 30
Switching NNRTI to Elvitegravir/c

STRATEGY-NNRTI

Study design

**Eligibility:**
- On NNRTI + FTC/TDF
- HIV-1 RNA <50 copies/mL for ≥6 months
- 1st or 2nd ART regimen
- No history of virological failure or resistance to FTC or TDF
- eGFR$_{CG}$ ≥70 mL/min

**Primary endpoint:** HIV-1 RNA <50 c/mL at Week 48 by Snapshot (noninferiority margin of 12%)

**Secondary endpoint:** Safety and tolerability at Week 48 & 96

ClinicalTrials.gov, number NCT01495702

Pozniak A et al. CROI 2014 Abstract #553LB
Switching NNRTI to Elvitegravir/c

STRATEGY-NNRTI

Previous ART regimens

<table>
<thead>
<tr>
<th>Single Tablet Regimen (n =338; 78%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atripla (n =322; 74%)</td>
</tr>
<tr>
<td>Eviplera (n =16; 4%)</td>
</tr>
</tbody>
</table>

NNRTI at Randomization (n =434)
- EFV 78%
- NVP 17%
- RPV 4%
- ETR <1%

Number of Prior Regimens (n =434)
- 1 regimen 91%
- 2 regimens 9%
- >2 regimens <1%

Reasons to enrol: (n=434)
- Simplification 48%
- Long-term toxicity concerns 20%
- Current tolerability issues 14%

EFV, efavirenz; ETR, etravirine; NNRTI, non-nucleoside reverse transcriptase inhibitors; NVP, nevirapine; RPV, rilpivirine

Pozniak A et al. CROI 2014 Abstract #553LB
Switching NNRTI to Elvitegravir/c

**STRATEGY-NNRTI**

Primary endpoint: HIV RNA<50 cps/ml

<table>
<thead>
<tr>
<th>CD4 Cell Count (cells/mm³)</th>
<th>Baseline (mean)</th>
<th>ΔWeek 48 (mean)</th>
<th>P-value (Δ W48 - BL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>E/C/F/TDF</td>
<td>586</td>
<td>+56</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NNRTI + FTC/TDF</td>
<td>593</td>
<td>+58</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Pozniak A et al. CROI 2014 Abstract #553LB
Switching NNRTI to Elvitegravir/c

STRATEGY-NNRTI

Patient-reported outcomes – EFV subgroup group analysis

Higher treatment satisfaction scores at Week 24 (mean: 21 vs. 14, p <0.001)^

* P <0.01 & **P <0.001 (comparison with baseline within treatment group).

Pozniak A et al. CROI 2014 Abstract #553LB
Use of Genvoya in renal dysfunction

Study 112 - phase III, 96-week, single-arm, open-label study of virologically suppressed adults with mild to moderate renal dysfunction switching to GENVOYA¹

**Inclusion criteria:**
– HIV-suppressed adults with renal impairment (CrCl 30–69 mL/min)
– HIV-1 RNA <50 copies/mL for ≥6 months
– CD4 ≥50 cells/mm³

**Primary endpoint:**
– Change from baseline in CrCl at Week 24**

![GENVOYA OD diagram]

**Primary endpoint**
- CrCl*
- aGFR† (n=32)

**Secondary endpoints**
- Wk 2, 4 or 8

**Median (Q1, Q3) change in CrCl from baseline to Week 24 was -0.4 (-4.8, 4.5) mL/min**


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*T Creatinine clearance (CrCl) measured using the Cockcroft-Gault formula in all patients
†Actual GFR measured using iohexol plasma clearance in a subset of patients at 3 time points: baseline; Week 2, 4 or 8; and Week 24

TDF, tenofovir disoproxil fumarate; OD, once daily; CrCl, creatinine clearance; aGFR, actual glomerular filtration rate

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Use of Genvoya in renal dysfunction

Antiretroviral Treatment Prior to Switching to E/C/F/TAF

- *Some regimens included >1 3rd agent; therefore, total >100%. ABC, abacavir; CCR5, C-C chemokine receptor type 5; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor.

Use of Genvoya in renal dysfunction

Primary endpoint change from baseline in CrCl at week 24
Genvoya maintains high rates of virological suppression at week 48

*Median (Q1, Q3) change in CrCl from baseline to Week 24 was -0.4 (-4.8, 4.5) mL/min

CrCl, creatinine clearance

Use of Genvoya in renal dysfunction

Statistically significant improvements in markers of renal tubular function at week 48
Improvements most notable in those switching from TDF-based ART

All total and TDF changes statistically significant; all non-TDF changes not statistically significant

Urine protein:creatinine ratio (uPCR)
Urine albumin:creatinine ratio (uACR)
Retinol-binding protein:creatinine ratio (RBP:Cr)
β-2-microglobulin:creatinine ratio (β2MG:Cr)

CrCl, creatinine clearance; TDF, tenofovir disoproxil fumarate

<table>
<thead>
<tr>
<th>HIV Patient Population</th>
<th>Study</th>
<th>N</th>
<th>Regimens and Specifics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-Naive Adults</td>
<td>292-0104</td>
<td>867</td>
<td>E/C/F/TAF vs. E/C/F/TDF</td>
</tr>
<tr>
<td>Treatment-Naive Adults</td>
<td>292-0111</td>
<td>866</td>
<td>E/C/F/TAF vs. E/C/F/TDF</td>
</tr>
<tr>
<td>Treatment-Naive Adolescents</td>
<td>292-0106</td>
<td>50</td>
<td>E/C/F/TAF 12-17 years</td>
</tr>
<tr>
<td>Virologically-Suppressed with ≥ 2 class historical resistance</td>
<td>292-0119</td>
<td>135</td>
<td>E/C/F/TAF + DRV vs. BR + DRV</td>
</tr>
<tr>
<td>Virologically-Suppressed</td>
<td>292-0109</td>
<td>1436</td>
<td>E/C/F/TAF vs. F/TDF +3rd ARV</td>
</tr>
<tr>
<td>Renal Impairment (mild to moderate)</td>
<td>292-0112</td>
<td>248</td>
<td>E/C/F/TAF eGFR 30-68 mL/min</td>
</tr>
<tr>
<td>HIV-1/HBV co-infected</td>
<td>292-1249</td>
<td>75</td>
<td>E/C/F/TAF</td>
</tr>
</tbody>
</table>

Callebaut et al. HIV Drug Therapy 2016. Abstract #0123
Virologic suppression was similar within each arm, regardless of the DRV dosage. However, E/C/F/TAF+DRV was statistically superior to staying on the Baseline Regimen.

Callebaut et al. HIV Drug Therapy 2016. Abstract #0123
Switching to InSTI as a ‘safer’ option

Raltegravir

Elvitegravir

Dolutegravir

200mg

Stribid

Genvoya

Dolutegravir

Triumeq
Dolutegravir – efficacy

DTG Phase III Clinical Trials in ART-Naïve subjects
FDA Snapshot (48-Week Data; Primary Endpoint)

In SINGLE, 414 patients received DTG +ABC/3TC.¹
In SPRING-2, on Day 1 in the DTG arm, 242 and 169 patients received TDF/FTC or ABC/3TC, respectively; in the RAL arm 247 and 164 patients received TDF/FTC and ABC/3TC, respectively.²
In FLAMINGO, on Day 1 in the DTG arm, 163 and 79 patients received TDF/FTC or ABC/3TC, respectively; in the DRV/r arm 162 and 80 patients received TDF/FTC and ABC/3TC, respectively.³

Higher responses on DTG + ABC/3TC vs EFV/TDF/FTC driven by withdrawals due to AEs (3% vs 11%, respectively)

Week 96 adjusted difference in response (95% CI): +8.0% (+2.3% to +13.8%); \( P=0.006 \)
Dolutegravir – efficacy

SINGLE Study
Virologic Suppression (HIV-1 RNA <50 c/mL; FDA Snapshot)

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>DTG + ABC/3TC QD (n=414)</th>
<th>EFV/TDF/FTC QD (n=419)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-related</td>
<td>184 (44%)</td>
<td>282 (67%)</td>
</tr>
<tr>
<td>Preferred term ≥10% in either arm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>29 (7%)</td>
<td>139 (33%)</td>
</tr>
<tr>
<td>Abnormal dreams</td>
<td>27 (7%)</td>
<td>66 (16%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>44 (11%)</td>
<td>49 (12%)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>41 (10%)</td>
<td>25 (6%)</td>
</tr>
<tr>
<td>Treatment-related Grades 2-4 (≥5% in either arm)</td>
<td>58 (14%)</td>
<td>116 (28%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2 (&lt;1%)</td>
<td>21 (5%)</td>
</tr>
</tbody>
</table>

Walmsley et al. CROI 2014; Boston, MA. Poster 337.
**VIKING Study design**

- Current or historic RAL-failures with evidence of RAL resistance
- At least 3 ART-class resistant (including INI)
- Subjects received DTG 50mg QD (Cohort I) and 50mg BID (Cohort II)
- Cohort II subjects should have ≥1 fully active ART in OBR

### Functional Monotherapy Phase

- Allocate to one of two groups based on genotype at screen to ensure broad sensitivity range
- Replace RAL with DTG or add, if RAL already stopped

### Continuation Phase

- DTG + OBR

### Timeline

- **Day 1**
- **Day 11**
- **Week 24**

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* Q148H/K/R plus changes in L74 and/or E138 and/or G140
** N155H and Y143H pathways or Q148H/K/R single mutants

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Soriano V et al. 13th EACS 2011
In an exploratory analysis* through Week 24, 11% and 38% of subjects receiving DTG 50 mg QD and BID respectively achieved <2 c/mL.

*Modified BioMerieux EasyQ HIV-1 SuperLow assay (lower limit of detection 2 c/mL)
DOL switch – treatment experienced

VIKING Study – responses by OBR activity

Baseline PSS of OBR

Increasing background drug activity remained as independent predictor of virologic response at Week 24 after adjusting for other variables

Soriano V et al. 13th EACS 2011
Dolutegravir / 3TC as a treatment option

**PADDLE** (Pilot Antiretroviral Design with Dolutegravir Lamivudine)
Phase IV, pilot, open-label, single arm exploratory trial

ARV-naïve patients, ≥18 years
HIV-1 RNA >5,000 copies/mL and ≤100,000 copies/mL
CD4 count ≥200 cells/mL
HB(s)Ag negative (n= 20)

Viral load was measured at baseline, days 2, 4, 7, 10, and weeks 2, 3, 4, 6, 8, 12, 24, 36 and 48*

* 96 week extension ongoing

# Dolutegravir / 3TC as a treatment option

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CD4 increase: Median (IQR) : 267 (180-462)

Dolutegravir and tolerability

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<th></th>
<th>Dolutegravir</th>
<th>Elvitegravir</th>
<th>Raltegravir</th>
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<td>Exposures on INSTI analysed, n</td>
<td>985</td>
<td>287</td>
<td>678</td>
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<td>Median Follow up per exposure, months (range)</td>
<td>11.5 (0-25.4)</td>
<td>16.0 (0.4-33.4)</td>
<td>36.3 (0.2-107.3)</td>
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<td>Alive and on INSTI at time of data cut, % (n)</td>
<td>91.0 % (896)</td>
<td>83.3 % (239)</td>
<td>54.0 % (366)</td>
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<td>Death while on INSTI, % (n)</td>
<td>0.9 % (9)</td>
<td>0.3 % (1)</td>
<td>4.7 % (32)</td>
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Reasons for discontinuation of INSTI (per exposure) over entire follow-up period

<table>
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<td>ART Simplification, % (n)</td>
<td>1.0 % (10)</td>
<td>2.8 % (8)</td>
<td>31.3 % (212)</td>
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<tr>
<td>Virological failure, % (n)</td>
<td>0.1 % (1)</td>
<td>1.7 % (5)</td>
<td>4.7 % (32)</td>
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<td>Other reasons, % (n)</td>
<td>0.2 % (2)</td>
<td>2.4 % (7)</td>
<td>1.5 % (8)</td>
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<td>Discontinuation due to AEs (any) total, % (n)</td>
<td><strong>6.8 % (67)</strong></td>
<td><strong>9.4 % (27)</strong></td>
<td><strong>4.1 % (28)</strong></td>
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Sabranski et al. HIV Drug Therapy, 2016. Abstract
# Dolutegravir and tolerability

## Discontinuation due to neuropsychiatric AEs

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<th>Elv (n=287)</th>
<th>Raltegravir (n=678)</th>
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<td>Neuropsychiatric % (n)</td>
<td>5.0 % (49)</td>
<td>1.0 % (3)</td>
<td>2.1 % (14)</td>
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<td>Insomnia, sleep disturbances</td>
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<tr>
<td>Poor concentration, slow thinking</td>
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<tr>
<td>Dizziness</td>
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<td>Headache, paraesthesia</td>
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<td>Depression</td>
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Log rank test p <0.0001

**Figure:**
- X-axis: Months on INSTI
- Y-axis: Survival probability
- DTG (n=985)
- Elv (n=287)
- Raltegravir (n=678)

**Graph:**
- shows cumulative survival over time for each INSTI group.
- Log rank test p <0.0001 indicates significant difference in discontinuation rates.
Switching for safety…what to know.

• Know your patient!!!
  Know the treatment history
  Is there transmitted / archived resistance?
  How is there adherence?

• Have a reason for switch
  Set your goals!

• Only switch in the setting of virological suppression

• Closely follow patients after switch

• Be aware of the consequences of getting it wrong!
  Resistance can be a disaster!
THANK YOU!

Paddy.mallon@ucd.ie
@HIVTox