4-3-2-1 and Less
Optimising Drug regimens in HIV

Anton Pozniak MD FRCP
Why optimise dosing?

- Less cost
- Less drug to be manufactured and stored
- Less chance of side effects
- Less pills
What about 4 Drug Therapy in ART Naive
REALITY Study: raltegravir-intensified quadruple therapy in first-line antiretroviral therapy

**Design**

- **Randomisation**
  - 1 : 1
  - Open label

- **Adults, adolescents and children > 5 years ARV-naïve CD4 < 100/mm³**

  - N = 902
    - 2 NRTI + NNRTI + 12 weeks of RAL

  - N = 903
    - 2 NRTI + NNRTI

- Two other factorial randomisations: 12 weeks enhanced prophylaxis, 12 weeks supplementary food

**Objective**

- Primary endpoint: 24-week mortality

Kityo C. AIDS 2016, Durban, Abs. FRAB0102LB
REALITY Study: raltegravir-intensified quadruple therapy in first-line antiretroviral therapy

**Mortality**

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<td>24</td>
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W24: HR = 1.09 (95% CI: 0.82-1.46) ; p = 0.54

**HIV RNA < 50 copies/mL (95% CI)**

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Mean change in CD4/mm³ at W48: + 163 vs + 148 (p = 0.04)
# 3 Drug therapy is Standard of Care in ART Naive

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What about the Efficacy of Dual versus Triple therapy – randomised studies
Dual versus Triple therapy – randomised studies

Nuke limiting Strategies
Analysing the efficacy of 2-drug versus 3-drug treatments

- PI/r + raltegravir
- PI/r + maraviroc
- PI/r + NRTI (mainly 3TC)
- DTG + 3TC
- DTG + RPV
- CTV + RPV
Overall, in 7 randomised trials of 1266 patients, PI/r + raltegravir showed HIV RNA suppression rates 10% lower than PI/r + 2NRTIs (p=0.008).

However there was evidence for heterogeneity between the trials (p=0.03).
Has PI/r plus integrase a role in Treatment experience?

**EARNEST and SECOND-LINE studies**

In treatment-experienced patients, RAL+LPV/r was non-inferior to 2NRTI+LPV/r

No efficacy advantage

No significant difference in number of Grade 3 or 4 adverse events

Costs of RAL+LPV/r significantly higher than 2NRTI+LPV/r in most countries
VL responses by randomized arm

Week 96 outcomes: Paton, NEJM 2014; 371; 234-47; Week 144 outcomes: Hakim, Poster 552, CROI 2015
3 randomised trials of **PI/r + maraviroc** versus PI/r + 2NRTIs

HIV RNA <50 copies/mL (switch = failure endpoint)

Overall, in 3 randomised trials of 967 patients, PI/r + maraviroc showed HIV RNA suppression rates 4% lower than PI/r + 2NRTIs.

This difference was outside the limits for non-inferiority (lower 95% confidence interval -15%)

There was evidence for heterogeneity between the trials (p=0.04).

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<td>Nozza et al.</td>
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<td>Total (95% CI)</td>
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<td>486</td>
<td>100.0%</td>
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Heterogeneity: Tau² = 0.01; Chi² = 6.61, df = 2 (P = 0.04); I² = 70%

Test for overall effect: Z = 0.74 (P = 0.46)
PI plus MVC
MARCH Study: switch to MVC

% with virologic response (HIV RNA < 200 c/mL), by week

Hazard ratio for loss of virological response < 200 c/mL over 48 weeks: 2.41 (95% CI: 1.31-4.43 ; p = 0.005) for the MVC + PI/r arm vs control arm

Number at risk

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<td>98</td>
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4 randomised trials of PI/r + NRTI versus PI/r + 2NRTIs
HIV RNA <50 copies/mL (switch = failure endpoint)

Overall, in 4 randomised trials of 1090 patients, PI/r + 3TC showed HIV RNA suppression rates 4% higher than PI/r + 2NRTIs

This difference was within the limits for non-inferiority (lower 95% confidence interval -1%) There was no evidence for heterogeneity between the trials (p=0.10).
2 Drugs in Naïve

GARDEL: Dual ART With LPV/RTV + 3TC vs Triple ART With LPV/RTV + 2 NRTIs

- Randomized, open-label phase III noninferiority trial
  - Primary endpoint: HIV-1 RNA < 50 c/mL (ITT-e, FDA snapshot analysis)

- Pts with virologic response at Wk 48 offered extension to Wk 96

Stratified by HIV-1 RNA
(≤ vs > 100,000 c/mL)

Wk 24 interim analysis
Wk 48 primary analysis
Wk 96 extension analysis

Lopinavir/Ritonavir 400/100 mg BID + Lamivudine 150 mg BID
(n = 217)

Lopinavir/Ritonavir 400/100 mg BID + Investigator-Selected NRTIs in FDC*
(n = 209)

*ZDV/3TC: 54%; TDF/FTC: 37%; ABC/3TC: 9%

ART-naive pats with HIV-1 RNA > 1000 copies/mL; no NRTI/PI resistance; HBsAg negative
(N = 426)

GARDEL: Dual ART Noninferior to Triple ART at Wk 48 and Wk 96

- Safety and tolerability also similar between treatment arms

**Virologic Success**
- Wk 48 difference: +4.6%
  (95% CI: -2.2 to 11.8; \( P = .171 \))
- Wk 96 difference: +5.9%
  (95% CI: -2.3 to 14.1; \( P = .165 \))

**Virologic Nonresponse**

**D/C due to AE or Death**

**D/C for Other Reasons**

Lets treat an Integrase like a boosted PI!

PADDLE: Dolutegravir + Lamivudine in Treatment-Naive Pts

- Open-label, single-arm phase IV exploratory trial
  - Primary endpoint: HIV-1 RNA < 50 copies/mL at Wk 48 (ITT-e, FDA snapshot analysis)

Treatment-naive pts with HIV-1 RNA 5000-100,000 copies/mL; CD4+ cell count ≥ 200 cells/mm³; HBsAg negative (N = 20)

First Cohort

DTG 50 mg QD + Lamivudine 300 mg QD (n = 10)

Second Cohort

Dolutegravir 50 mg QD + Lamivudine 300 mg QD (n = 10)

Second cohort to be enrolled following confirmation of first cohort success at Wk 8

# PADDLE Study: Efficacy-DTG and 3TC in Naïve patients

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SAE = serious adverse event  
PDVF = protocol defined virologic failure

Cahn P, et al. AIDS 2016; Durban, South Africa; July 18-22, 2016; Abst. FARBO104LB.
ANRS 167 LamiDol Study
DTG/3TC Maintenance

- 110 Subjects
- No Hx of failure, No Hep B
- 8 week Switch to 2NRTI+DTG
- Then to DTG/3TC-40 Weeks FU

- 97% (101/104) pts maintained therapeutic success through 40 wks of dual therapy (study Wk 48)[1]
  - No INSTI resistance in 3 pts with virologic failure
  - 7 pts with serious AEs, only 2 related to dual therapy

Switch to 2 drugs
-do we need nukes?
SWORD 1 & 2: Switch From Suppressive ART to DTG + RPV Dual Therapy

- Randomized, open-label, multicenter phase III trials
  - Primary endpoint: HIV-1 RNA < 50 copies/mL at Wk 48 (ITT-E snapshot)

- 70% to 73% of pts receiving TDF at baseline

HIV-infected pts with HIV-1 RNA < 50 c/mL for ≥ 12 mos while receiving first-line or second-line ART with 2 NRTIs + INSTI, NNRTI, or PI; no previous VF; HBV negative (N = 1024)

Llibre JM, et al. CROI 2017. Abstract 44LB.
Switch From Suppressive ART to DTG + RPV
Noninferior to Continued Baseline ART at Wk 48

- 1 pt with confirmed criteria for virologic withdrawal at Wk 36 in DTG + RPV arm had K101K/E (1.2-fold RPV change)
  - Resuppressed with continued DTG + RPV
  - No INSTI resistance

- AE rates generally similar between treatment arms through Wk 52
  - Numerically higher rate of drug-related grade 1/2 AEs with switch: 17% vs 2%
  - Numerically higher rate of withdrawal for AEs with switch: 4% vs < 1%

Llibre JM, et al. CROI 2017. Abstract 44LB.
Switch to DTG + RPV in Suppressed Pts With Multiple Previous Treatment Failures

- Open-label cohort study based in clinical practice setting (N = 38)
  - DTG 50 mg/day + RPV 25 mg/day for pts with long-term virologic suppression but virologic failure on > 1 previous ART regimens

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<th>Baseline Characteristic</th>
<th>Switch to DTG + RPV (N = 38)</th>
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<td>NRTI + NNRTI + PI + INSTI</td>
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<td>Reasons for switch to DTG + RPV</td>
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<td>Drug–drug interaction</td>
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<td>Toxicity</td>
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<td>Simplification</td>
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<td>Pre-existing resistance mutations</td>
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<tr>
<td>NRTI: 65; NNRTI: 37; PI: 32; INSTI: NA</td>
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- HIV-1 RNA suppressed to < 35 copies/mL in 92% (35/38) at Wk 48
  - No virologic failures; 3 pts d/c (GI toxicity, DDI, physician decision, n = 1)

- DTG + RPV associated with improved liver function tests, improved lipid profile, and stable kidney function at Wk 48

Induction period

Maintenance period

CAB 400 mg IM + RPV 600 mg IM
Q4W (n=115)

CAB 600 mg IM + RPV 900 mg IM
Q8W (n=115)

CAB 30 mg + ABC/3TC PO QD (n=56)

CAB loading dose at Day 1

CAB loading doses at Day 1 and Week 4

Add RPV PO QD
4 weeks

Day 1
Randomization
2:2:1

Week 32
Primary analysis
Dosing regimen selection

Week 48
Analysis
Dosing regimen confirmation

ABC/3TC, abacavir/lamivudine; ALT, alanine aminotransferase; IM, intramuscular; PO, orally; QD, once daily; Q4W, every 4 weeks; Q8W, every 8 weeks; ULN, upper limit of normal. aSubjects who withdrew after at least 1 IM dose entered the long-term follow-up period.
bSubjects can elect to enter Q4W and Q8W LA Extension Phase beyond Week 96.

Margolis et al. AIDS 2016; Durban, South Africa. Abstract THAB0206LB.
HIV-1 RNA <50 c/mL at Week 48: ITT-ME (Snapshot)

Virologic outcomes

<table>
<thead>
<tr>
<th>Virologic success</th>
<th>Virologic non-response</th>
<th>No virologic data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q8W (n=115)</td>
<td>Q4W (n=115)</td>
<td>CAB 744 (n=56)</td>
</tr>
<tr>
<td>92</td>
<td>91</td>
<td>89</td>
</tr>
<tr>
<td>7</td>
<td>&lt;1</td>
<td>2</td>
</tr>
<tr>
<td>&lt;1</td>
<td></td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9</td>
</tr>
</tbody>
</table>

Both Q8W and Q4W comparable to Oral CAB at Week 48

Met prespecified threshold for concluding IM regimen is comparable to oral regimen (Bayesian Posterior Probability >90% that true IM response rate is no worse than -10% compared to the oral regimen). Observed Bayesian Probabilities: Q8W vs Oral = 99.7%; Q4W vs Oral = 99.4%.

Margolis et al. AIDS 2016; Durban, South Africa. Abstract THAB0206LB.
Protocol-Defined Virologic Failure (PDVF)

### Maintenance period

<table>
<thead>
<tr>
<th>Subjects with PDVF</th>
<th>Q8W IM (n=115)</th>
<th>Q4W IM (n=115)</th>
<th>Oral CAB (n=56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>INI-r mutations</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>NRTI-r mutations</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>NNRTI-r mutations</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

- **NNRTI**—**K103N, E138G, and K238T** (FC RPV=3.3; Etravirine=1.9); **INI**—**Q148R** (FC CAB=5.1; Dolutegravir=1.38)
- No additional PDVFs beyond W48 on any arm (all subjects through W72)

PDVF: <1.0 log<sub>10</sub> c/mL decrease in plasma HIV-1 RNA by Week 4, OR confirmed HIV-1 RNA ≥200 c/mL after prior suppression to <200 c/mL, OR >0.5 log<sub>10</sub> c/mL increase from nadir HIV-1 RNA value ≥200 c/mL. aOne additional PDVF without treatment-emergent resistance occurred during oral Induction Period due to oral medication non-adherence. bOne PDVF at Week 4: no detectable RPV at Week 4 and Week 8, suggesting maladministration. cOne PDVF at Week 48 at HIV-1 RNA 463 c/mL (confirmed at 205 c/mL). dContains data beyond W48.
2 drugs

Health Warning!

Not in Hepatitis B co-infected

? Pregnancy

? TB
PI monotherapy
MONET: Switch to DRV/RTV vs DRV/RTV + 2 NRTIs
Primary endpoint: HIV-1 RNA<50 copies/mL

Proportion of subjects with HIV-1 RNA<50 copies/mL by Week 144

- For patients with HIV RNA < 50 mL/min at baseline, switching to DRV/RTV monotherapy did not show noninferior efficacy to DRV/RTV plus two NRTIs in an ITT/TLOVR analysis, but not in a strict ITT analysis (switches not considered failures)

* Intent to treat (ITT), TLOVR, switch = failure method; † strict ITT analysis (switches not considered failures)

DRV, darunavir; ITT, intent-to-treat; NRTI, nucleoside reverse transcriptase inhibitors; RTV, ritonavir
Switching to DRV/RTV monotherapy showed lower efficacy vs triple antiretroviral therapy at Week 48 in the primary switch equals failure analysis (difference -8.8%, 95% CI: -15.5 to -1.8)

There was no evidence of PI resistance

CI, confidence interval; DRV, darunavir; ITT, intent-to-treat; N(t)RTI, nucleo(t)side reverse transcriptase inhibitor; PI, protease inhibitor; RTV, ritonavir

Antinori A et al. HIV12 2014; Glasgow, Scotland. #O423A
PI Monotherapy - predictors of response

Predicted probabilities of Response - Mono Therapy

- 95% Upper CI
- Probability of response
- 95% Lower CI

CD4+ Nadir (count)
Previous NNRTI use (Y/N)

Ripamonti et al CROI 2015 poster 551
INSTI monotherapy
Methods DOMONO

Randomized open label multicenter

Dolutegravir monotherapy 50 mg for 48 weeks with or without a meal

If HIV-RNA becomes detectable (any level >20c/ml) the patient is instructed to take DTG with a meal

Key inclusion:

- HIV-RNA < 1,0^E5
- CD4-nadir ≥ 200
- HIV-RNA <50 ≥24w
- Never failed
- No resistance
- HBV immune
- >95% estimated compliance

Results secondary endpoint 1: Week 24 <50 c/ml DTG monotherapy versus cART

DTG n=46/50 (92%)  
cART n=53/53 (100%)  
\{ p=0.052  
Delta 8% (95% C.I. -1% to +19%) (*)

Wijting I et al, HIV Glasgow 2016
Emergent INSTI Resistance After Switch to DTG Monotherapy

- International, multicenter retrospective study
  - Evaluated virologically suppressed pts switched to DTG 50 mg QD monotherapy
  - Pts with history of VF on INSTI and INSTI resistance excluded
- 11 of 122 pts switched to DTG monotherapy experienced VF
  - 9 of 11 had genotypic INSTI resistance at VF

- INSTI resistance pathways varied

<table>
<thead>
<tr>
<th>INSTI Resistance at VF</th>
</tr>
</thead>
<tbody>
<tr>
<td>92Q/155H (n = 1)</td>
</tr>
<tr>
<td>97A/155H (n = 1)</td>
</tr>
<tr>
<td>155H/148R (n = 1)</td>
</tr>
<tr>
<td>118R (n = 2)</td>
</tr>
<tr>
<td>148K (n = 1)</td>
</tr>
<tr>
<td>148H (n = 2)</td>
</tr>
<tr>
<td>148R (n = 1)</td>
</tr>
</tbody>
</table>

LESS
Lower doses
Can we Save EFV?

Dose Reduction of EFV

ENCORE1: 400-mg EFV non-inferior to 600-mg EFV With TDF/FTC for Initial ART

- Randomized, double-blind, placebo-controlled, non-inferiority phase III trial
  - Part of ongoing effort to identify ARVs effective at lower doses (and cost)

- No significant difference in SAEs between treatment arms

- More pts with study drug-related AEs for EFV 600 mg vs EFV 400 mg (47.2% vs 36.8%; p=0.008)

- More pts discontinued EFV 600 mg due to AE vs EFV 400 mg (1.9% vs 5.8%; p=0.010)

Puls, R et al. IAS 2013. Abstract WELBB01
PI dose optimisation

Atazanavir/r: 200/100 mg OD dose?

Darunavir/r: 400/100 OD dose?

Cobicistat as alternative to ritonavir?
LASA trial: Maintenance trial, primary analysis at Week 48

HIV RNA <50 on ART
n=560

ATV/r 200/100 mg OD + 2NRTIs
n=280

ATV/r 300/100 mg OD + 2NRTIs
n=280

<50 copies/mL were: 93.4% vs 91.7% (95% CI: 1.71, -2.67 to 6.09).

Patients enrolled in Thailand. (HIV RNA suppression endpoint)
DRV/r: can we switch to a 400/100 OD dose?

• Approved dose is 600/100 mg BID for PI pre-treated patients, 800/100 OD for PI naïve patients
Cmin for DRV/r 400/100 versus 800/100 OD
POWER 1 and 2 trials: Cmin 32% lower for 400/100 OD versus 800/100 dose

Sekar et al, EACS, CROI 2006 [abstr J121]
POWER trials: %HIV RNA >1 log reduction at Week 24, by dose and baseline DRV resistance

**DRV FC <4 (sensitive)**

**DRV FC >4 (resistant)**

**DRV/r dose group**

Haubrich et al AIDS 2007, 21: F11-F18
TITAN trial: HIV RNA <50 copies/mL at Week 48, Treatment experienced, PI sensitive patients, DRV/r 600/100 mg BID +2NRTIs, by DRV Cmin

Sekar et al, EACS, Madrid 2007 [abstr P4.1/10]
ODIN trial – safety results to Week 48
DRV/r 800/100 OD versus 600/100 BID

<table>
<thead>
<tr>
<th>Safety parameter</th>
<th>800/100 OD</th>
<th>600/100 BID</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=294</td>
<td>n=296</td>
<td></td>
</tr>
<tr>
<td>≥1 Grade 3 or 4 AE</td>
<td>23 (8%)</td>
<td>45 (15%)</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>D/C for adverse events</td>
<td>10 (3%)</td>
<td>14 (5%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Triglycerides ≥500mg/dL</td>
<td>15 (5%)</td>
<td>31 (11%)</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Total cholesterol ≥240mg/dL</td>
<td>29 (10%)</td>
<td>58 (21%)</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>LDL cholesterol ≥160mg/dL</td>
<td>28 (10%)</td>
<td>47 (17%)</td>
<td>p&lt;0.05</td>
</tr>
</tbody>
</table>

No other significant differences in lab parameters or individual clinical adverse events

Cahn et al. AIDS 2011, 25:929-939
Study endpoints

- The proportion of patients with HIV-1 RNA <50 c/mL at w48 (ITT).
  Non inferiority if lower limit of the 95% CI for \( \delta < -15\% \), 80% power
- Changes in CD4+ T cell count
- Changes in DRV C\(_{\text{trough}}\) in plasma
- The proportion of patients with AEs during follow-up
- The economic cost derived from ARV drugs
DRV600. Results at w48
Non inferiority of DRV/r 600/100 mg QD

% HIV-1 RNA <50 cp/mL

<table>
<thead>
<tr>
<th></th>
<th>ITT</th>
<th>Observed data</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRV800</td>
<td>50</td>
<td>49</td>
</tr>
<tr>
<td>DRV600</td>
<td>50</td>
<td>48</td>
</tr>
</tbody>
</table>

95% CI for the difference:

- ITT: -4.0 (-12.9; 4.9)
- Observed data: -2.2 (-9.6; 5.2)
Similar to Cobi?

DRV/r 400/100 OD versus DRV/c 800/150 OD

POWER trials  Mathias 2010  Kakuda 2014

Mean Cmin (ng/mL)

<table>
<thead>
<tr>
<th></th>
<th>DRV/r 800/100</th>
<th>DRV/r 400/100</th>
<th>DRV/r 800/100</th>
<th>DRV/c 800/150</th>
<th>DRV/r 800/100</th>
<th>DRV/c 800/150</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1840</td>
<td>1258</td>
<td>1870</td>
<td>1330</td>
<td>1540</td>
<td>1224</td>
</tr>
</tbody>
</table>

Mathias 2010

Kakuda 2014
Conclusion

1. No clinical advantage of 4 drugs-even in low CD4 and high VL.

2. Need RT inhibitors plus high barrier to resistance in 2 drug Rx

3. Dual therapy Regimen in naïve or switch-some data evolving

4. Monotherapy is a niche area but only with boosted Pis not InSTIs

5. Stay with the data use triple therapy and wait for trials to report.

6. Low dose EFV approved by the FDA

7. ? move to low dose DRV