Clinical Case Presentation

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Case 1: HIV summary (1)

• 36-year-old male
• First seen at another hospital because of HIV infection being detected on entry into military service in 2001
• Baseline plasma HIV RNA load (PVL), >1,000,000 copies/ml; CD4, 155 cells/mm$^3$
• No opportunistic illness or hepatitis coinfection
HIV summary (2)

• Zidovudine/lamivudine (coformulated Combivir) and efavirenz were begun in 2001
  – PVL declined to <400 copies/ml 5 months of initiation of combination antiretroviral therapy (cART)
  – PVL remained <400 copies/ml on subsequent 6 testing occasions between 2002 and 2004
  – He was lost to follow-up in 2005

• He presented with cytomegalovirus (CMV) retinitis in January 2009, with PVL, 795,000 copies/ml and CD4, 34 cells/mm³
Viral re-suppression and detection of drug resistance following interruption of a suppressive nNRTI-based regimen

- Interruption of nNRTI-based regimens in SMART study
  - simultaneous; staggered (temporarily continuing NRTIs); switch (to PI/2NRTIs before complete interruption)
- 601/688 (87.4%) achieved re-suppression
  - Staggered vs. simultaneous: AOR, 1.94 (1.02-3.69)
  - Switch vs. simultaneous: AOR, 3.64 (1.37-9.64)
- NNRTI mutations detected
  - Simultaneous: 16.4%
  - Staggered: 12.5%
  - Switch: 4.2%

EARNEST: Second-line LPV/RTV ± RAL or 2-3 NRTIs in PI-Naive Pts

- Randomized, open-label, multicenter phase III trial in sub-Saharan Africa

**HIV-infected pts >12 yrs of age with confirmed VF on NNRTI + 2 NRTIs and no prior PIs (N = 1277)**

Stratified by study center, CD4+ cell count (< 200 vs ≥ 200 cells/mm³)

- LPV/RTV + RAL (n = 433)
- LPV/RTV + 2-3 NRTIs* (n = 426)
- LPV/RTV + RAL (n = 418)
- LPV/RTV Monotherapy (n = 418)

Wk 12

LPV/RTV 400/100 mg and RAL 400 mg dosed BID.

*New or recycled NRTIs chosen WITHOUT genotype by clinician.


Slide credit: clinicaloptions.com
EARNEST: Boosted PI + RAL Comparable to Boosted PI + NRTIs

- SECOND-LINE and ACTG 5273 showed similar results

HIV summary (3)

- Abacavir/3TC + boosted lopinavir (Kaletra) were begun
- Occasions of poor adherence were reported
- Counseling was provided to improve adherence to the regimen
HIV summary (4)

- Viral rebound was detected in October 2016, when the PVL was 16,500 copies/ml.
## Drug resistance interpretation (Oct 2016)

<table>
<thead>
<tr>
<th></th>
<th>Protease</th>
<th>Reverse transcriptase</th>
<th>Integrase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>NRTI</td>
<td>nNRTI</td>
</tr>
<tr>
<td>Major resistance-associated mutations</td>
<td>None</td>
<td>M184V</td>
<td>G190GA</td>
</tr>
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<td>Drug Susceptibility</td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>High-level</td>
<td></td>
<td>3TC; FTC</td>
<td>NVP</td>
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<td>Intermediate-level</td>
<td></td>
<td></td>
<td>EFV</td>
</tr>
<tr>
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<td></td>
<td>ABC</td>
<td>RPV</td>
</tr>
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<td>Potential low-level</td>
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<td>ddl</td>
<td>ETR</td>
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<td>RAL; EVG; DTG</td>
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**Abbreviations:** 3TC, lamivudine; ABC, abacavir; ATV, atazanavir; AZT, zidovudine; d4T, stavudine; ddl, didanosine; DRV, darunavir; DTG, dolutegravir; EFV, efavirenz; EVG, elvitegravir; ETR, etravirine; FTC, emtricitabine; LPV, lopinavir; NVP, nevirapine; r, ritonavir; RAL, raltegravir; RPV, rilpivirine
Genetic barrier to emergence of resistance mutations

HIV summary (5)

- Viral rebound was detected in October 2016, when the PVL was 16,500 copies/ml
- CART was switched to TDF/FTC plus dolutegravir on 5 Jan, 2017 and PVL <20 copies/ml was achieved on 25 May, 2017

RAMs: M184V; G190GA
Case 2: HIV summary (1)

- A 33-year-old male patient received a diagnosis of HIV infection with baseline PVL of 186,000 copies/ml and CD4, 46 cells/mm$^3$ in late 2013
- CART with TDF, 3TC, and nevirapine was begun in Dec 2013
  - PVL was 39,200 copies/ml 1 month later
Case 2: HIV summary (2)

- CART with TDF, 3TC, and nevirapine was begun on 10 Dec 2013 – PVL was 39200 copies/ml 1 month later – PVL decreased by <1.0 log_{10} copies/ml
- CART was switched to Combivir plus boosted atazanavir on 2 Jan, 2014

<table>
<thead>
<tr>
<th>Resistance Level</th>
<th>Protease</th>
<th>NRTI</th>
<th>nNRTI</th>
<th>InSTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-level</td>
<td>ABC; ddl; TDF</td>
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<td></td>
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**Diagram:**
- **No RAM**
- TDF/FTC + NVP
- Combivir + boosted atazanavir
- **K65KR; Y181C**

**Graph:**
- Y-axis: 0, 1, 2, 3, 4, 5, 6
- X-axis: 1-1-00, 1-2-00, 1-3-00, 1-4-00
SECOND-LINE trial: Design

On 1st line 2NRTI+ NNRTI for ≥24 wk Virological failure (PVL >500 c/mL) X 2

no previous exposure to protease inhibitors (PIs) or integrase strand transfer inhibitors (InSTIs)

LPV/r 400/100 mg BID + 2–3 NRTIs

(n=270)

LPV/r 400/100 mg BID + RAL

(n=271)

0 48 96 weeks

Primary endpoint:
HIV RNA <50 c/mL at week 48

Monitoring:
CD4 + VL at each visit (12-weekly)

Hypothesis:
PI/RAL non-inferior to PI/NRTI, margin 12%

Second-Line Study: VL suppression at Week 48

HIV summary (3)

• CART was switched to zidovudine/lamivudine (Combivir) plus boosted atazanavir
  – He was not able to tolerate zidovudine/lamivudine
  – Viral rebound prompted the switch to Kaletra + raltegravir, which resulted in viral suppression

• Switch to dolutegravir (DTG) + boosted darunavir because of intolerance of diarrhea on 23 Feb, 2017
Case 3: HIV summary (1)

- A 47-year-old male was seen because of virological failure
  - Previous and current regimens
    - AZT/3TC (Combivir) + Kaletra (2006/2/7-2012/7/10)
    - ABC/3TC (Kivexa) + Kaletra (2012/7/10-)
  - Hyperlipidemia (total cholesterol, 283 mg/dl); smoking

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<table>
<thead>
<tr>
<th>Date</th>
<th>ABC/3TC + Kaletra</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-1-00</td>
<td>2</td>
</tr>
<tr>
<td>1-2-00</td>
<td>3</td>
</tr>
<tr>
<td>1-3-00</td>
<td>4</td>
</tr>
</tbody>
</table>
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Drug resistance interpretation (2013/8/16)

<table>
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<th>Protease</th>
<th>Reverse transcriptase</th>
<th>Integrase</th>
</tr>
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<tbody>
<tr>
<td>M46L; I50V; I54V; V82A</td>
<td></td>
<td>V75I; M184V</td>
<td>None</td>
</tr>
</tbody>
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Salvage regimens available

- **ANRS TRIO trial**
  - **Entry criteria:**
    - Plasma HIV RNA load >1000 copies/ml; a history of failures while on NNRTIs
    - ≥3 primary RAMs to protease inhibitors and NRTIs, ≤3 RAMs to darunavir and NNRTIs
  - 103 patients with number of primary RAMs to PI (n=4), NNRTI (1), and NRTI (6)
  - 90 patients (87%) received optimized background regimen
    - 12 enfuvirtide; 86 NRTIs

Case 3: HIV summary (2)

• Switched to salvage cART on 29 October, 2013
  – Raltegravir (400 mg) + Etravirine (100 mg) + Darunavir (600 mg)/ritonavir (100 mg), all being twice daily dosing
  – Add-on atrovastatin (20 mg), followed by switch to rosuvastatin

• He had tolerated the “RED” regimen well with sustained viral suppression
  – Hyperlipidemia improved, but not resolved
  – Twice daily dosing made life a bit difficult
SAILING: phase III trial in treatment-EXPERIENCED, INI-NAÏVE subjects

- ARV-experienced, INI-naïve adults
- HIV-1 RNA ≥400 c/mL*
- Resistance to ≥2 classes of ARVs (not incl. INIs)
- Stratified by HIV-1 RNA (≤ or >50,000), DRV/r use and no. of fully active drugs in OBR

Primary endpoint: proportion of subjects with HIV-1 RNA <50 c/mL at Week 48

*With 2 consecutive HIV-1 RNA ≥400 c/mL, unless screening HIV-1 RNA >1,000 c/mL

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>DTG 50 mg QD (n=354)</th>
<th>RAL 400 mg BID (n=361)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, median (years)</strong></td>
<td>42</td>
<td>43</td>
</tr>
<tr>
<td><strong>Gender, female</strong></td>
<td>30%</td>
<td>34%</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>49%</td>
<td>48%</td>
</tr>
<tr>
<td>African American or African heritage</td>
<td>40%</td>
<td>44%</td>
</tr>
<tr>
<td><strong>HIV-1 RNA, median ($\log_{10}$ c/mL)</strong></td>
<td>4.17</td>
<td>4.21</td>
</tr>
<tr>
<td>&gt;50,000 c/mL</td>
<td>30%</td>
<td>30%</td>
</tr>
<tr>
<td><strong>CD4+ count, median (cells/mm$^3$)</strong></td>
<td>205</td>
<td>193</td>
</tr>
<tr>
<td><strong>HBV coinfection</strong></td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td><strong>HCV coinfection</strong></td>
<td>9%</td>
<td>13%</td>
</tr>
<tr>
<td><strong>Duration prior ART, median (months)</strong></td>
<td>80</td>
<td>72</td>
</tr>
<tr>
<td>≥3 class resistance</td>
<td>47%</td>
<td>51%</td>
</tr>
<tr>
<td><strong>Most common background regimens, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DRV/r, TDF</td>
<td>62 (18)</td>
<td>73 (20)</td>
</tr>
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<td>LPV/r, TDF</td>
<td>40 (11)</td>
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</tr>
<tr>
<td><strong>DRV/r, ETR</strong></td>
<td>33 (9)</td>
<td>40 (11)</td>
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<tr>
<td>LPV/r</td>
<td>36 (10)</td>
<td>35 (10)</td>
</tr>
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<td>ATV/r, TDF</td>
<td>37 (10)</td>
<td>33 (9)</td>
</tr>
<tr>
<td>DRV/r, MVC</td>
<td>23 (6)</td>
<td>19 (5)</td>
</tr>
</tbody>
</table>

ATV, atazanavir; ETR, etravirine; HBV, hepatitis B virus; HCV, hepatitis C virus; LPV, lopinavir; MVC, maraviroc

Snapshot analysis of proportion of patients with plasma HIV-1 RNA <50 copies/ml by visits

Week 48 adjusted difference\(^\dagger\) in response (95% CI):
+7.4 in favour of DTG (0.7%, 14.2%)

Mean (SD) CD4+ change from baseline to Week 48 was similar between arms: DTG: +162 (151) cells/mm\(^3\); RAL: +153 (144) cells/mm\(^3\)

ABC/3TC + Kaletra

Raltegravir + Etravirine + Darunavir (600)/r (100) bid, “RED”

Date: 2013/8/16

<table>
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<tr>
<th>Drug Susceptibility</th>
<th>PI</th>
<th>NRTI</th>
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<tr>
<td>High-level</td>
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</table>
Summary

• In patients who fail the first-line regimens containing 2NRTIs plus nNRTI, a regimen commonly used in the Asia-Pacific region, switch to boosted PI (Kaletra) plus 2-3 NRTIs or boosted PI (Kaletra) plus raltegravir provides effective options in achieving high rates of viral suppression.

• In patients with emergent resistance mutations to PIs, NRTIs, and nNRTIs, optimizing background regimens, identified by genotypic resistance testing, with the addition of an INSTI is effective in re-suppressing viral replication.
Thank you
## Global burden of TDR

**Sequence-Level Meta-Analysis**

<table>
<thead>
<tr>
<th>TDR studies</th>
<th>sub-Saharan Africa (n=95)</th>
<th>south/SE Asia (n= 56)</th>
<th>Latin America/Caribbean (n= 38)</th>
<th>Europe (n= 42)</th>
<th>North America (n= 27)</th>
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<tbody>
<tr>
<td>Overall</td>
<td>2.8%</td>
<td>2.9%</td>
<td>7.6%</td>
<td>9.4%</td>
<td>11.5%</td>
<td>5.6%</td>
<td>4.0%</td>
</tr>
<tr>
<td>NRTI</td>
<td>0%</td>
<td>1%</td>
<td>4%</td>
<td>5.6%</td>
<td>5.8%</td>
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**TDR and ART scale-up:**

7/56 pre-scale-up: 2.9% (2, >5%)

49/56 post-scale-up: 3.0% (15, >5%)

↑Overall TDR (0.97-fold), NNRTI (1.09-fold), PI (0.97-fold) resistance, NRTI (0.93-fold) (all P>0.05)

# Global burden of TDR

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<td>1.6%</td>
<td>0.2%</td>
</tr>
</tbody>
</table>

**Upper-Income Asian Countries**

- Japan, Korea, Taiwan

↑Overall TDR (1.15-fold), NNRTI (1.33-fold), PI resistance

### Pre-treatment Drug Resistance in Asia

<table>
<thead>
<tr>
<th>Location</th>
<th>Sample Size</th>
<th>Dates</th>
<th>NRTI (%)</th>
<th>nNRTI (%)</th>
<th>PI (%)</th>
<th>II (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turkey (n=117; 2009-12)</td>
<td>7.6%</td>
<td>4.2% NRTI; 1.7% nNRTI; 1.7% PI</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Iran (n=47/30; 2010-11)</td>
<td>4.3% NRTI/6.7% nNRTI</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>India (n=51, antenatal)</td>
<td>2%</td>
<td>nNRTI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>India (n=105 children; 2007-2011)</td>
<td>5.7% (2% NRTI; 4.8% nNRTI)</td>
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<td></td>
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</tr>
<tr>
<td>TASER-M (n=1471; 2007-2010)</td>
<td>4.1% (2.4% NRTI; 1.7% nNRTI; 0.7%, PI)</td>
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</tr>
<tr>
<td>Vietnam (n=1389; 2008-12)</td>
<td>4.18% (2.02% NRTI; 1.7% nNRTI; 1.08% PI)</td>
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<tr>
<td>Malaysia (n=100; 2008-2010)</td>
<td>0%</td>
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</tr>
<tr>
<td>Taiwan (n=1970; 2012-2014)</td>
<td>14.3% (3.6% NRTI; 9.8% nNRTI; 2.3% PI; 3.1% II)</td>
<td></td>
<td></td>
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<tr>
<td>Korea (50; 2007-11)</td>
<td>10.0% (10% nNRTI)</td>
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<tr>
<td>Nagoya (149 MSM; 2008-9)</td>
<td>7.8% (6.0% NRTI; 0% nNRTI; 10.1% PI)</td>
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<td></td>
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</tr>
<tr>
<td>Beijing (536 MSM; 2008-11)</td>
<td>7.8% (0.9% NRTI; 1.7% nNRTI; 6.2% PI)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>7 cities (441 MSM; 2012-13)</td>
<td>4.6% (2.7% NRTI; 0.5% nNRTI; 2.2% PI)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Vietnam (n=1389; 2008-12)</td>
<td>4.18% (2.02% NRTI; 1.7% nNRTI; 1.08% PI)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Beijing (536 MSM; 2008-11)</td>
<td>7.8% (0.9% NRTI; 1.7% nNRTI; 6.2% PI)</td>
<td></td>
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</tr>
<tr>
<td>7 cities (441 MSM; 2012-13)</td>
<td>4.6% (2.7% NRTI; 0.5% nNRTI; 2.2% PI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Korea (50; 2007-11)</td>
<td>10.0% (10% nNRTI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nagoya (149 MSM; 2008-9)</td>
<td>7.8% (6.0% NRTI; 0% nNRTI; 10.1% PI)</td>
<td></td>
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<td>Nagoya (149 MSM; 2008-9)</td>
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<td></td>
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</tr>
</tbody>
</table>
Emerging trends of HIV drug resistance in Chinese HIV-infected patients receiving first-line HAART: a systematic review and meta-analysis

12 longitudinal cohorts and 13 cross-sectional studies included
Acquired drug resistance of HIV-1 at first-line ART failure in Asia

- 97 (92%) harboring $\geq 1$ RAM at first-line failure
- 39 (37%) multi-NRTI RAMs:
  - 6 with Q151M
  - 24 with $\geq 2$ TAMs
  - 32 with M184V + $\geq 1$ TAM

Associated factors with multi-NRTI RAMs:
- CD4 $\leq 200$ cells/μl at genotyping (OR, 4.43)
- ART duration $>2$ years (OR, 6.25)

Included: patients with HIV resistant to 3 classes of drug and who were failing ART
RAL vs placebo: favorable long-term efficacy

### LANDMARK SIMPLIFICATION TRIALS OF TRIPLE THERAPY: LESSONS

<table>
<thead>
<tr>
<th>Year</th>
<th>Trial</th>
<th>Control</th>
<th>Experimental</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>SWITCHMRK**</td>
<td>2 NRTI + LPV/r</td>
<td>2 NRTI + RAL</td>
<td>RAL ↓ response.</td>
</tr>
<tr>
<td>2010</td>
<td>SPIRAL**</td>
<td>2 NRTI + bPI</td>
<td>2 NRTI + RAL</td>
<td>Non-inferior response</td>
</tr>
</tbody>
</table>

*Enrolled patients with archived NRTI resistance
*Switch to a lower genetic barrier combination

---

### IMPACT OF PRIOR TREATMENT FAILURE ON MAINTENANCE OF SUPPRESSION

<table>
<thead>
<tr>
<th>TRIAL</th>
<th>RAL</th>
<th>LPV/r or bPI</th>
<th>DIFFERENCE</th>
<th>MONTHS &lt; 50 c/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>SWITCHMRK</td>
<td>76.6%</td>
<td>91.9%</td>
<td>-15.3% (-24.9 to -6.2)</td>
<td>≥ 3 (median ?)</td>
</tr>
<tr>
<td>SPIRAL</td>
<td>88.6%</td>
<td>83.1%</td>
<td>5.5 (-5.9 to 17)</td>
<td>≥ 6 (median 73)</td>
</tr>
</tbody>
</table>

**DURATION OF SUPPRESSION PROBABLY MATTERS**

VL suppression at 96 weeks

PI/RAL vs PI/NRTI  P=0.36
PI-mono+ vs PI/NRTI  P=0.002

<table>
<thead>
<tr>
<th>Threshold</th>
<th>PI/NRTI</th>
<th>PI/RAL</th>
<th>PI-mono+</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10000 c/ml</td>
<td>91%</td>
<td>93%</td>
<td>83%</td>
</tr>
<tr>
<td>&lt;1000 c/ml</td>
<td>88%</td>
<td>87%</td>
<td>67%</td>
</tr>
<tr>
<td>&lt;400 c/ml</td>
<td>86%</td>
<td>86%</td>
<td>61%</td>
</tr>
<tr>
<td>&lt;50 c/ml</td>
<td>74%</td>
<td>73%</td>
<td>44%</td>
</tr>
</tbody>
</table>

P-values: P=0.36 (PI/RAL vs PI/NRTI), P=0.002 (PI-mono+ vs PI/NRTI), P<0.0001 (PI-mono+ vs PI/NRTI for all thresholds)
SECOND-LINE trial: Resistance

<table>
<thead>
<tr>
<th></th>
<th>LPV/r + 2–3 N(t)RTI</th>
<th>LPV/r + RAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants analyzed for genotyping</td>
<td>55</td>
<td>49</td>
</tr>
<tr>
<td>Participants with data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protease and reverse transcriptase</td>
<td>43</td>
<td>42</td>
</tr>
<tr>
<td>Integrase</td>
<td>46</td>
<td>47</td>
</tr>
<tr>
<td>No new resistance mutations in protease, reverse transcriptase, or integrase</td>
<td>37/43 (86.0%)</td>
<td>39/47 (83.0%)</td>
</tr>
<tr>
<td>NtRTI-associated mutations</td>
<td>6/43 (14.0%)</td>
<td>0/42 (0.0%)</td>
</tr>
<tr>
<td>M184V</td>
<td>2/43 (4.7%)</td>
<td>0/42 (0.0%)</td>
</tr>
<tr>
<td>TAM</td>
<td>2/43 (4.7%)</td>
<td>0/42 (0.0%)</td>
</tr>
<tr>
<td>L65A or L70G</td>
<td>0/43 (0.0%)</td>
<td>0/42 (0.0%)</td>
</tr>
<tr>
<td>69 insertion complex</td>
<td>2/43 (4.7%)</td>
<td>0/42 (0.0%)</td>
</tr>
<tr>
<td>151 insertion complex</td>
<td>1/43 (2.3%)</td>
<td>0/42 (0.0%)</td>
</tr>
<tr>
<td>Protease inhibitor-associated mutations</td>
<td>0/43 (0.0%)</td>
<td>0/47 (0.0%)</td>
</tr>
<tr>
<td>Integrase strand transfer inhibitor-associated mutations</td>
<td>0/46 (0.0%)</td>
<td>7/47 (14.9%)</td>
</tr>
<tr>
<td>T66A</td>
<td>0/46 (0.0%)</td>
<td>1/47 (2.1%)</td>
</tr>
<tr>
<td>T143A or T143C or T143H</td>
<td>0/46 (0.0%)</td>
<td>1/47 (2.1%)</td>
</tr>
<tr>
<td>A155H</td>
<td>0/46 (0.0%)</td>
<td>5/47 (10.6%)</td>
</tr>
</tbody>
</table>
VIKING-3: Dolutegravir After Failure of Integrase Inhibitor–Based Regimen

- Phase III single-arm trial

  Pts with HIV-1 RNA ≥ 500 c/mL, RAL and/or EVG resistance, and resistance to ≥ 2 other antiretroviral classes* (N = 183)

  Dolutegravir 50 mg BID + Continue Failing Regimen

  Day 8

  Dolutegravir 50 mg BID + Optimized Background Regimen With Overall Susceptibility Score ≥ 1 (ie, ≥ 1 active drug)

  Wk 24

  Wk 48

  Functional Monotherapy

  Optimized Therapy

- Mean HIV-1 RNA change from baseline to Day 8
  - Overall: \(-1.4 \log_{10} \text{copies/mL (} P < .001)\)
  - No primary integrase resistance mutations at BL: \(-1.6 \log_{10} \text{copies/mL}\)
  - Q148 + ≤ 1 secondary integrase resistance mutation: \(-1.1 \log_{10} \text{copies/mL}\)
  - Q148 + ≥ 2 secondary integrase resistance mutations: \(-1.0 \log_{10} \text{copies/mL}\)

*Detected at screening or based on historical evidence.

VIKING-3: Efficacy of DTG in INSTI-Experienced Pts at Wk 48

- 24-wk data on full cohort (N = 183) and 48-wk data on first 114 pts
- Response rates affected by baseline INSTI resistance but not overall susceptibility score of background regimen

**Outcome, n (%)**

<table>
<thead>
<tr>
<th></th>
<th>Wk 24 (n = 183)</th>
<th>Wk 48 (n = 114)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-1 RNA &lt; 50 c/mL at Wk 24 (snapshot, ITT-E)</td>
<td>126 (69)</td>
<td>64 (56)</td>
</tr>
<tr>
<td>Virologic nonresponse</td>
<td>50 (27)</td>
<td>44 (39)</td>
</tr>
<tr>
<td>d/c due to AE or death</td>
<td>5 (3)</td>
<td>5 (4)</td>
</tr>
</tbody>
</table>

**HIV-1 RNA < 50 c/mL at Wk 24 by INSTI Mutation(s), n/N (%)**

<table>
<thead>
<tr>
<th>INSTI Mutation(s)</th>
<th>0</th>
<th>1</th>
<th>≥ 2</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Q148</td>
<td>4/4 (100)</td>
<td>35/40 (83)</td>
<td>57/70 (76)</td>
<td>96/114 (79)</td>
</tr>
<tr>
<td>Q148 + 1</td>
<td>2/2 (100)</td>
<td>8/12 (67)</td>
<td>10/17 (59)</td>
<td>20/31 (65)</td>
</tr>
<tr>
<td>Q148 + ≥ 2</td>
<td>1/2 (50)</td>
<td>2/11 (18)</td>
<td>1/3 (33)</td>
<td>4/16 (25)</td>
</tr>
</tbody>
</table>

SPIRAL: Switch From RTV-Boosted PIs to RAL in Virologically Suppressed Patients

- Randomized, open-label, multicenter study
- Median duration of virologic suppression before switch: 6.6 yrs

Stratified by use of lipid-lowering agents (yes vs no)

Patients on stable RTV-boosted PI therapy, HIV-1 RNA < 50 copies/mL for ≥ 6 mos (N = 273)

- Switch Boosted PI to RAL 400 mg BID + maintain other BL antiretroviral agents (n = 139)
- Continue Boosted PI-Based Regimen* (n = 134)

SPIRAL: Switch to RAL Noninferior to Maintaining Boosted PI Regimens

Free of Treatment Failure at Wk 48 (ITT, Switch = Failure)

Patients With VF

<table>
<thead>
<tr>
<th></th>
<th>RAL (n = 4)</th>
<th>PI/RTV (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior VF</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Prior suboptimal ART</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Prior resistance mutations</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Resistance test at VF</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>- Mutations</td>
<td>0</td>
<td>3 (PR, RT)</td>
</tr>
</tbody>
</table>

Mean Change From Baseline to Wk 48, %

<table>
<thead>
<tr>
<th></th>
<th>Switch to RAL</th>
<th>Continue PI/RTV</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglycerides</td>
<td>-22.1</td>
<td>+4.7</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>TC</td>
<td>-11.2</td>
<td>+1.8</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>LDL-C</td>
<td>-6.5</td>
<td>+3.0</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>HDL-C</td>
<td>-3.2</td>
<td>+5.8</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Total to HDL-C ratio</td>
<td>-4.9</td>
<td>-1.3</td>
<td>&lt; .05</td>
</tr>
</tbody>
</table>

SWITCHMRK: Switch to RAL from LPV/RTV in Pts With Viral Suppression

- HIV-infected patients with viral suppression on LPV/RTV-based ART for ≥ 3 mos (N = 702) (SWITCHMRK 1: 348 SWITCHMRK 2: 354)
- Stratified by duration of LPV/RTV use (≤ 1 yr vs > 1 yr), age, race, sex, region, hepatitis B and C
- Wk 12 lipid analysis
- Wk 24 efficacy analysis
- Switch to Raltegravir 400 mg BID + other BL antiretroviral agents* (SWITCHMRK 1: n = 174 SWITCHMRK 2: n = 176)
- Continue Lopinavir/Ritonavir 200 mg/50 mg BID + other BL antiretroviral agents* (SWITCHMRK 1: n = 174 SWITCHMRK 2: n = 178)

*All patients continued background regimen including ≥ 2 NRTIs.

SWITCHMRK: Main Findings

- RAL did not meet efficacy noninferiority criteria vs continued LPV/RTV at Wk 24; study terminated
  - However, comparable efficacy between arms among patients receiving LPV/RTV as first regimen at study entry

<table>
<thead>
<tr>
<th>Outcome</th>
<th>SWITCHMRK 1</th>
<th>SWITCHMRK 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RAL (n = 174)</td>
<td>LPV/RTV (n = 174)</td>
</tr>
<tr>
<td>All patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-1 RNA &lt; 50 copies/mL at Wk 24, %</td>
<td>80.8</td>
<td>87.4</td>
</tr>
<tr>
<td>Treatment difference, % (95% CI)</td>
<td>-6.6 (-14.4 to 1.2)</td>
<td>-5.8 (-12.2 to 0.2)</td>
</tr>
<tr>
<td>Patients receiving LPV/RTV as first regimen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-1 RNA &lt; 50 copies/mL at Wk 24, %</td>
<td>86.1</td>
<td>86.7</td>
</tr>
<tr>
<td>Treatment difference, % (95% CI)</td>
<td>-0.6 (-12.2 to 10.9)</td>
<td>-5.3 (-16.9 to 5.7)</td>
</tr>
</tbody>
</table>

SWITCHMRK: Main Findings

- Inferior efficacy of RAL appeared driven by higher failure rate among patients with previous virologic failure

<table>
<thead>
<tr>
<th>Outcome</th>
<th>SWITCHMRK1</th>
<th>SWITCHMRK2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RAL (n = 174)</td>
<td>LPV/RTV (n = 174)</td>
</tr>
<tr>
<td>Patients without previous virologic failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-1 RNA &lt; 50 copies/mL at Wk 24, %</td>
<td>85.1</td>
<td>85.8</td>
</tr>
<tr>
<td>Treatment difference, % (95% CI)</td>
<td>-0.7 (-9.9 to 8.6)</td>
<td>-1.0 (-8.5 to 6.3)</td>
</tr>
<tr>
<td>Patients with previous virologic failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-1 RNA &lt; 50 copies/mL at Wk 24, %</td>
<td>72.3</td>
<td>89.7</td>
</tr>
<tr>
<td>Treatment difference, % (95% CI)</td>
<td>-17.3 (-33.0 to -2.5)</td>
<td>-14.2 (-26.5 to -2.6)</td>
</tr>
</tbody>
</table>