Antiretroviral Treatment Strategies: Clinical Case Presentation

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Disclosure

• No conflicts of interests.
Case 1  Mr. Wang

- 33 year-old man, MSM
- Diagnosed with HIV infection in May, 2013 during routine anonymous screening test every 6 months
- Previous history of secondary syphilis 6 months before HIV diagnosis
- Occupation: school teacher
- Baseline CD4: 369 cells/uL, HIV VL: 30300 copies/ml
- HBsAg(-), anti-HBs Ab(+), anti-HBc (-), anti-HCV (-)
- Deferred cART due to the concerns about adverse effects
Treatment course

- Gradually declined CD4 cell count during follow-up
  - Started with TDF+3TC+NVP since Apr. 03, 2014
  - Baseline genotypic resistance test: no resistance associated mutations (RAM)
  - May 01, 2014: CD4: 378 cells/μL, VL: 358 copies/ml
  - Tolerated the cART well
  - Impaired adherence thereafter: missing doses 3-7 times per month
  - Check genotypic resistance test because of virologic failure
Summary of the resistance associated mutation:

• NRTI: K65R
  • Only AZT fully susceptible

• NNRTI: Y181C and V179E
  • No active NNRTI available

• Protease inhibitor: No major mutation detected

• Integrase inhibitor: not done, but very low transmitted drug resistance was ever identified during surveillance (<1%)
How to choose regimen after virologic failure?

- Ideally, a new ARV regimen should contain at least two, and preferably three, fully active drugs whose predicted activity is based on the patient's drug treatment history, resistance testing, or the mechanistic action of a new drug class (AI).

What regimen can we choose in the presentation of K65R and Y181C?
- AZT/3TC + PI/r ?
- AZT/3TC + DTG ?
- AZT(with or without 3TC) + RAL + PI/r ?
- AZT(with or without 3TC) + DTG + PI/r ?
- RAL (or DTG) + PI/r ?

DHHS guideline, July 2016
Treatment course

• Dec. 06, 2014: switched to AZT/3TC + ATV/r
• The regimen was tolerated
• Jan. 03, 2015: CD4: 322 cells/uL, VL: 481 copies/ml (Hb: 11.8 gm/dL)
• Mar. 03, 2015: CD4: 363 cells/uL, VL: 71 copies/ml (Hb: 9.8 gm/dL)
• Dizzy and pale appearance in May 2015 => Hb: 5.8 gm/dL
• Switched to RAL + ATV/r

Does ATV/r + RAL work?
SPARTAN: Pilot Study of ATV + RAL vs ATV/RTV + TDF/FTC in Naive Patients

- Randomized, noncomparative, open-label, multicenter pilot study in treatment-naive patients with HIV-1 RNA $\geq 5000$ copies/mL
  - ATV 300 mg BID + RAL 400 mg BID (n = 63) vs
  - ATV/RTV 300/100 mg QD + TDF/FTC 300/200 mg QD (n = 31)
- Mean Baseline HIV-1 RNA: 4.9 log$_{10}$ copies/mL

Primary Endpoint: HIV-1 RNA < 50 copies/mL Through Wk 24 (CVR*, NC = F)

ATV BID + RAL BID ATP/RTV QD + TDF/FTC

*CVR = modified ITT

SPARTAN: Week 24 results

- Trial terminated at week 24 due to resistance data and grade 4 bilirubin abnormalities (21%) with experimental regimen vs control arm (0%)

<table>
<thead>
<tr>
<th>Resistance Through Wk 24, n</th>
<th>ATV + RAL (n = 63)</th>
<th>ATV/RTV + TDF/FTC (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virologic failure (HIV-1 RNA &gt; 50 copies/mL)</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>BL HIV-1 RNA &gt; 250,000 copies/mL</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Evaluable for resistance testing* (HIV-1 RNA &gt; 400 copies/mL)</td>
<td>6</td>
<td>1</td>
</tr>
</tbody>
</table>

Genotypic and phenotypic RAL resistance
- N155H | 2 | NA |
- Q148R | 1 | NA |
- Q148R + N155H + T97A | 1 | NA |

Phenotypic RAL resistance without genotypic evidence of resistance | 1 | NA |

ATV resistance | 0 | 0 |
TDF/FTC resistance | NA | 0 |

*Criteria for resistance testing:
- HIV-1 RNA ≥ 400 copies/mL at or after Wk 24
- Rebound to HIV-1 RNA ≥ 400 any time during the study
- Discontinued before achieving HIV-1 RNA < 50 copies/mL after Wk 8 with last HIV RNA ≥ 400 copies/mL

HARNESS study: ritonavir-boosted atazanavir (ATV/r)+raltegravir (RAL) switch study in virologically suppressed, HIV-1-infected patients

Figure 1. Study Design

Experimental group (N=72)
ATV/r 300/100mg QD + RAL 400mg BID

Reference group (N=37)
ATV/r 300/100mg QD + TDF/FTC 300/200mg QD

Virologically suppressed (<40 copies/mL) HIV-infected adults who had been receiving two NRTIs + any third agent and who were experiencing safety and/or tolerability issues

2:1 Randomization (N=109)

Screening period no more than 30 days

Day 14: Baseline
Week 12: stopping rule 1
Week 24: Primary endpoint & stopping rule 2
Week 48: Final analysis

ATV/r, ritonavir-boosted atazanavir; BID, twice daily; FTC, emtricitabine; NRTI, nucleoside reverse transcriptase inhibitors; QD, once daily; RAL, raltegravir; TDF, tenofovir disoproxil fumarate

Primary outcome – Efficacy at Week 24
- At week 24, the proportions of patients with stable HIV-1 RNA levels of <40 copies/mL (primary endpoint) were 80.6% in the experimental group and 94.6% in the reference group, by ITT analysis (Figure 2)
- At the Week 24 assessment, CD4+ cell counts had increased from baseline levels to 618 (SD 239) and 661 (SD 282) cells/mm³ in the ATV/r+RAL and ATV/r+TDF/FTC treatment groups, respectively; corresponding absolute increases from baseline in CD4+ counts were 30 and 30 cells/mm³, respectively

Figure 2. Proportions of Patients with HIV-1 RNA levels of <40 copies/mL (primary endpoint) at Week 24

Secondary Outcomes – Efficacy at Week 48
- At Week 48, 56 (77.8%) and 32 (86.5%) of patients in the ATV/r+RAL and ATV/r+TDF/FTC treatment groups, respectively, completed the study. Proportions of patients with HIV-1 RNA levels of <40 copies/mL are presented in Figure 3
- At Week 48, CD4+ cell counts had increased from baseline to 674 (SD 255) and 666 (SD 296) cells/mm³ in the ATV/r+RAL and ATV/r+TDF/FTC treatment groups, respectively; corresponding absolute increases from baseline in CD4+ counts were 86 and 35 cells/mm³, respectively

Figure 3. Proportions of Patients with HIV-1 RNA levels of <40 copies/mL at Week 48

Treatment course

• Switched to RAL + ATV/r
  • Jun. 01, 2015: CD4: 494 cells/µL, VL: <20 copies/ml, T-bil: 5.1 mg/dL
  • Concerns about the appearance

• Switched to RAL + DRV/r due to hyperbilirubinemia
  • Aug. 28, 2015: CD4: 565 cells/µL, VL: <20 copies/ml, T-bil: 0.8 mg/dL
  • The virus was suppressed as well thereafter
EARNEST: Second-line LPV/RTV-Based ART After Initial NNRTI Failure

- Randomized, controlled, open-label, phase III trial

HIV-infected adults and adolescents received first-line NNRTI-based ART > 12 mos, > 90% adherence in previous mo, treatment failure by WHO (2010) criteria* (N = 1277)

Baseline demographics (medians): HIV-1 RNA 69,782 copies/mL; CD4+ 71 cells/mm³; time on ART 4 years

*Including clinical, CD4+ cell count (HIV-1 RNA confirmed), or virologic criteria.
†Selected by physician according to local standard of care.

EARNEST: Clinical Outcomes at week 96

- **Primary endpoints**: good disease control at week 96

- “Good disease control” at Wk 96 defined as pt alive, no new WHO 4 events from Wks 0-96, and CD4+ cell count > 250 cells/mm³, and HIV-1 RNA < 10,000 copies/mL or > 10,000 copies/mL without PI resistance mutations

EARNEST: Paradoxical Relationship Between Resistance and VL Suppression

- Number of predicted “active” NRTIs in prescribed second-line Rx:
  - 0: 230 (59%)
  - 1: 128 (33%)
  - ≥2: 33 (8%)
- NRTI predicted active if no int./high level resistance by Stanford

Summary

• Scenario of NRTIs and NNRTI regimen failure with resistance

• Dual therapy (PI/r plus RAL) had been proved same efficacy (EARNEST and SECOND-LINE trial) as NRTIs + PI/r in the scenario of NNRTI-based regimen failure
  • ATV/r plus integrase inhibitor currently not a good choice according to the clinical trials

• DHHS guideline: PI/r + ETR or DTG could possible be options
Case 2  Mr. Lee

• 28 year-old man, MSM
• HIV infection diagnosed in July 2013 in anonymous screening
• No previous STDs
• Occupation: office worker
• HBsAg (+), anti-HBs (-), anti-HBc (+), anti-HCV (-)
• Baseline CD4: 789 cells/uL, VL: 463000 copies/ml
• Deferred ART because of preserved immunity
Treatment course

• Mar. 24, 2015: CD4: 451 cells/uL, VL: 436000 copies/ml

• Start TDF+3TC+EFV on Apr. 21, 2015
  • Allergic reaction 10 days later, ART discontinued due to severe drug eruption → EFV related?
  • The drug eruption subsided after ART discontinued
  • Baseline genotypic resistance test available on May 03, 2015
Summary of the resistance associated mutation:

- **NRTI: No RAM**
  - all susceptible

- **NNRTI: Y188HY**
  - RPV, ETR susceptible

- **Protease inhibitor: M46IM**
  - DRV/r fully susceptible
  - Potential low-level resistant: ATV/r, LPV/r

- **Integrase inhibitor: not done, but very low transmitted drug resistance was ever identified during surveillance (<1%)**
RPV-based regimen?


HIV-1 RNA < 50 copies/mL (%)

By Baseline CD4+ Count (cells/mm³)

By Baseline HIV-1 RNA (copies/mL)
Treatment course

• s/p TDF+3TC + LPV/r on May 05, 2015
  • Drug eruption developed again
    => Allergy to TDF? or 3TC? or LPV/r?

• What would be the next choice?

• We re-challenged with 3TC during outpatient clinics after drug eruption subsided
  • skin rash developed 2 hours later
Treatment course

- Restarted with LPV/r + RAL on Jun. 09, 2015, tolerated well
  - Add TDF on Jun. 16, 2015 for hepatitis B
    - HBV baseline viral load: 20,300 IU/ml
  - ART regimen: TDF + RAL + LPV/r
  - 2015/07/14 CD4: 770 cells/uL, VL: 155 copies/ml
  - 2015/10/13 CD4: 780 cells/uL, VL: 23 copies/ml
  - The virus remained suppressed till 2017/04
For HIV/HBV co-infected patients

- All persons with HBV/HIV co-infection should receive ART including TDF + 3TC or FTC unless history of TDF intolerance.

- If TDF is strictly contra-indicated, entecavir + adefovir may be tried.

EACS guideline v8.0, Oct. 2015
Case 2 Summary

• A case with chronic hepatitis B, RAM of 1st generation NNRTI and partial RAM of PI, allergy to backbone NRTI
  • Dual therapy with PI/r plus INSTI may be used when backbone NRTIs were not able to use
  • TDF should be reserved for chronic hepatitis B if no strictly contraindication
Thanks for your attention