New Drugs, Management of Treatment-experienced Patients, and Other Fun Facts from CROI 2014

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NEAETC

← New hospital-approved logo!
CROI 2014 in Boston and The Winter That Would Never End

<table>
<thead>
<tr>
<th></th>
<th>Actual Temp</th>
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</thead>
<tbody>
<tr>
<td>3</td>
<td>30° Lo 16°</td>
<td>4</td>
<td>31° Lo 12°</td>
<td>5</td>
<td>29° Lo 20°</td>
<td>6</td>
<td>25° Lo 11°</td>
<td>7</td>
<td>34° Lo 16°</td>
</tr>
</tbody>
</table>

Major storm pummels mid-Atlantic, cancels hundreds of flights
New Drugs, New Strategies
Question

• We already have five non-nucleoside reverse transcriptase inhibitors – nevirapine, delavirdine, efavirenz, etravirine, and rilpivirine. Do we need another?

A. Yes
B. No
## NNRTIs: Nobody’s Perfect

<table>
<thead>
<tr>
<th>NNRTI (in order of FDA approval)</th>
<th>Weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nevirapine</td>
<td>Potential fatal hypersensitivity; dose escalation needed</td>
</tr>
<tr>
<td>Delavirdine</td>
<td>Numerous</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>CNS toxicity; possible teratogenicity; rash; hyperlipidemia; K103N most common transmitted drug resistance mutation</td>
</tr>
<tr>
<td>Etravirine</td>
<td>Twice daily as FDA-approved; gritty formulation; drug-drug interactions</td>
</tr>
<tr>
<td>Rilpivirine</td>
<td>Suboptimal activity at high viral load, low CD4; food requirement; no PPIs; E138K</td>
</tr>
</tbody>
</table>
Doravirine (MK-1439)

- Potent in-vitro antiviral activity,
- PK supports QD dosing
- <3-fold potency shift vs. common NNRTI-resistance mutants (K103N, Y181C, G190A, E138K)
- Low potential for CNS effects
- Few drug-drug interactions predicted
- Lower protein-binding vs. other NNRTIs
Doravirine (MK-1439) Phase II

PART 1
Dose-Ranging
~200 patients
(~40/group)

24 Week Primary Time Point for Dose Selection

96 Week End of Study Treatment for Part 1

MK-1439 25 mg
MK-1439 50 mg
MK-1439 100 mg
MK-1439 200 mg

MK-1439 Selected Dose

Efavirenz

Efavirenz

Morales-Ramirez J, et al. 21st CROI; Boston, MA; March 3-6, 2014. Abst. 92LB.
Doravirine vs EFV Phase II: 24 Week Results

MK-1439 all doses combined: 76.4%

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Percentage</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>MK-1439 25 mg</td>
<td>32/40</td>
<td>80.0</td>
<td></td>
</tr>
<tr>
<td>MK-1439 50 mg</td>
<td>32/42</td>
<td>76.2</td>
<td></td>
</tr>
<tr>
<td>MK-1439 100 mg</td>
<td>30/40</td>
<td>71.4</td>
<td></td>
</tr>
<tr>
<td>MK-1439 200 mg</td>
<td>32/41</td>
<td>78.0</td>
<td></td>
</tr>
<tr>
<td>Efavirenz 600 mg</td>
<td>27/42</td>
<td>64.3</td>
<td></td>
</tr>
</tbody>
</table>

Morales-Ramirez J, et al. 21st CROI; Boston, MA; March 3-6, 2014. Abst. 92LB.
• Conducted at 38 sites, 13 countries, n=630
• 94% vs 92% had HIV RNA < 200 at week 48 for 400 and 600 mg dose, respectively
• Drug-related adverse effects significantly more common in the standard-dose group
• Implications for future use?

ENCORE Study Group, Lancet 2014.
Question about Doravirine

• What is the optimal comparator for the phase III study?
  – TDF/FTC/EFV?
  – TDF/FTC/RPV? Would need to exclude patients with HIV RNA > 100K
  – TDF/FTC (or ABC/3TC) + dolutegravir?
Drugs with Novel Mechanisms for Pan-Resistant HIV in Phase II or Later

• BMS-663068 (attachment inhibitor)
• ... that’s it!

Critical for patients with highly resistant virus to preserve virologic suppression through excellent adherence!

Lalezari J, et al. 21st CROI; Boston, MA; March 3-6, 2014. Abst. 86.
AI438011: BMS-663068 Monotherapy Substudy: Mean Change in HIV-1 RNA from Baseline*

*Error bars represent standard error of the mean.

Lalezari J, et al. 21st CROI; Boston, MA; March 3-6, 2014. Abst. 86.
Prevalence of Drug Resistance Mutations in Treatment-Naive Patients, 2000-2013

- Baseline plasma samples from 4 phase III trials (GS 903, 934, 104, 111)
  - 1617 samples analyzed for integrase mutations
  - 2531 analyzed for protease or RT mutations
- Little evidence of transmitted INSTI resistance over period
- Stable prevalence of NRTI resistance (mostly TAMs)
  - M184V/I ≤ 0.2%
  - K65R ≤ 0.2%
- Substantial increase in prevalence of NNRTI resistance, modest increase in PI resistance
- INSTI resistance T97A polymorphism

Question

- A significant fraction of my patients would prefer getting a once-monthly injection to taking a pill every day.

1. True
2. False
Long-Acting ART for Maintenance Therapy

• GSK1265744 (744): Investigational integrase inhibitor
  – Closely related to dolutegravir
• Rilpivirine: approved NNRTI for initial therapy
• Both being developed as long-acting injectable formulations
• Can a two-drug regimen of oral 744 and rilpivirine maintain virologic suppression?
LATTE: Study Design

- Phase IIb, randomized, multicenter, partially blind, dose-ranging study comparing S/GSK744 plus RPV to EFV plus NRTIs

**HIV ART-naïve**
HIV RNA >1,000 c/mL
1:1:1:1 Randomization
Stratified by VL and NRTI

**Oral Induction Phase**
- 744 10 mg + 2 NRTIs*
- 744 30 mg + 2 NRTIs*
- 744 60 mg + 2 NRTIs*

**Oral Maintenance Phase**
- 744 10 mg + RPV 25 mg
- 744 30 mg + RPV 25 mg
- 744 60 mg + RPV 25 mg

**EFV 600 mg + 2 NRTIs***

*ABC/3TC or TDF/FTC
**Patients on 744 + NRTI: If week 20 VL <50 c/mL - simplify to 744/RPV at week 24

Two-drug 744 + RPV maintained Suppression Comparable to EFV-based Therapy

744 overall response W24: 87%
EFV response W24: 74%

744 overall response W48: 82%
EFV response W48: 71%

Median (IQR) change from baseline CD4+ cell count (cells/mm³)

- Week 48:
  - 744 overall: +219 (141,343)
  - EFV: +227 (134,369)

- Week 24:
  - 744 overall: +219 (141,343)
  - EFV: +227 (134,369)

- Week 12:
  - 744 overall: +219 (141,343)
  - EFV: +227 (134,369)

- Week 8:
  - 744 overall: +219 (141,343)
  - EFV: +227 (134,369)

- Week 4:
  - 744 overall: +219 (141,343)
  - EFV: +227 (134,369)

- Week 2:
  - 744 overall: +219 (141,343)
  - EFV: +227 (134,369)

- Baseline (BL):
  - 744 overall: +219 (141,343)
  - EFV: +227 (134,369)
## Protocol-Defined Virologic Failure and Resistance

<table>
<thead>
<tr>
<th>Subjects with PDVF during Induction</th>
<th>744 total n=181</th>
<th>EFV n=62</th>
</tr>
</thead>
<tbody>
<tr>
<td>*1 subject per 744 dose</td>
<td>3* (2%)</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>No NRTI, NNRTI or INI treatment-emergent mutations</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subjects with PDVF during Maintenance</th>
<th>744 total n=160</th>
<th>EFV n=47</th>
</tr>
</thead>
<tbody>
<tr>
<td>2** (1%)</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td><strong>IN genotypic results at BL and time of PDVF</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>INI-r mutations</strong></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>PR/RT genotypic results at BL and time of</strong></td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>PDVF</strong></td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><strong>NRTI-r mutations</strong></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>NNRTI-r mutations</strong></td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

**PDVF:** *<1.0 log$_{10}$ c/mL decrease in plasma HIV-1 RNA by Week 4*  
**OR** confirmed HIV-1 RNA ≥200 c/mL at or after Week 16 or after prior suppression to <200 c/mL

**744 10 mg – treatment emergent INI (Q148R) and NNRTI (E138Q) at W48; 744 FC = 3; RPV FC = 2**  
- 744 and RPV concentrations <50% of expected; **extreme calorie restricted diet W40-W48**

**744 30 mg – PDVF at W36; no treatment-emergent mutations**

*Margolis et al. CROI 2014; Boston, MA. Abstract 91LB.*
LATTE Study:
Conclusions and Implications

• Dual therapy with 744 and rilpivirine maintained virologic suppression
• Both are being actively investigated as long-acting intramuscular injections
• Clinical trials of this combination for treatment (and 744 alone for PrEP) are planned
• Resistance implications of missed doses?
Question

- In patients who are virologically suppressed on treatment, I may recommend switching the regimen to improve safety, tolerability, and convenience.

1. Yes I do – especially for older regimens.
2. No – don’t rock the boat, if it ain’t broke, etc.
Boosted PI to TDF/FTC/EVG/c

STRATEGY-PI Study

E/C/F/TDF: co-formulated elvitegravir 150 mg, cobicistat 150 mg, emtricitabine 200 mg, tenofovir DF 300 mg. PI + RTV + FTC/TDF: ritonavir-boosted PI and emtricitabine/tenofovir DF.

Reasons subject choose to enroll in study

<table>
<thead>
<tr>
<th>Reason</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Desire to simplify current regimen</td>
<td>86%</td>
</tr>
<tr>
<td>Concerned about long-term side effects of current regimen</td>
<td>12%</td>
</tr>
</tbody>
</table>

Arribas J, et al. 21st CROI; Boston, MA; March 3-6, 2014. Abst. 551LB.
<table>
<thead>
<tr>
<th></th>
<th>E/C/F/TDF (n =290)</th>
<th>PI + RTV + FTC/TDF (n =139)</th>
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<tbody>
<tr>
<td><strong>Virologic Success at Week 48</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-1 RNA &lt;50 copies/mL*</td>
<td>272 (93.8%)</td>
<td>121 (87.1%)</td>
</tr>
<tr>
<td><strong>Virologic Failure (VF) at Week 48</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-1 RNA ≥ 50 copies/mL</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Discontinued study drug due to lack of efficacy</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Discontinued study drug due to other reasons and last available HIV-1 RNA ≥50 copies/mL</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>No Virologic Data in Week 48 Window</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discontinued study drug due to AE</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Discontinued study drug due to other reasons and last available HIV-1 RNA &lt;50 copies/mL</td>
<td>11</td>
<td>14</td>
</tr>
<tr>
<td>Missing data during window but on study drug</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

No subject met the protocol defined criteria for treatment-emergent resistance testing with virologic rebound ≥400 c/mL

* 6.7% (+0.4%, +13.7%) *P*=0.025 for superiority
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, $P < 0.001$)

* $P < 0.04$ & ** $P < 0.001$ (comparison with baseline within each treatment group). Decreases noted at week 4 & sustained to week 48.

$P < 0.001$, diarrhea & $P=0.019$, bloating (comparison of changes from baseline at week 48 between treatment group).

† HIV Treatment Satisfaction questionnaire, score range: -30 to 30

Arribas J, et al. 21st CROI; Boston, MA; March 3-6, 2014. Abst. 551LB.
Switch to TDF/FTC/EVG/c

- Two prospective studies validate the safety of this practice
  - Maintains virologic suppression
  - May improve regimen tolerability, compliance
- Caution regarding
  - Baseline renal function (no eGFR < 70)
  - Extensive NRTI resistance
  - Drug-drug interactions due to cobicistat

Arribas J, et al. 21st CROI; Boston, MA; March 3-6, 2014. Abst. 551LB; Pozniak A, et al. 21st CROI; Boston, MA; March 3-6, 2014. Abst. 553LB
Comorbidities
D:A:D: Abacavir Remains Associated With Elevated Risk of MI

- Update of analysis of ABC and risk of acute MI in pts with low, medium, and high CVD risk
- After initial D:A:D report in March 2008, decline in ABC initiations in pts with higher CVD risk

<table>
<thead>
<tr>
<th>Framingham Risk Group</th>
<th>ABC Use as Proportion of All ART Initiations, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before March 2008</td>
<td></td>
</tr>
<tr>
<td>Low/unknown CVD risk</td>
<td>13.6</td>
</tr>
<tr>
<td>Moderate/high CVD risk</td>
<td>17.1</td>
</tr>
<tr>
<td>After March 2008</td>
<td></td>
</tr>
<tr>
<td>Low/unknown CVD risk</td>
<td>7.6</td>
</tr>
<tr>
<td>Moderate/high CVD risk</td>
<td>5.3</td>
</tr>
</tbody>
</table>

D:A:D: Abacavir Remains Associated With Elevated Risk of MI

- Analysis of MI risk with ABC pre and post 3/08 in D:A:D cohort
- There were trends to less ABC use in high risk individuals post 3/08
- MI rates
  - Current/Recent ABC 0.47 (0.42-0.52)/1000 pt yrs of FU
  - No ABC 0.21 (0.19-0.22)/1000 pt yrs of FU
- RR with ABC 1.98 (1.72-2.29), Pre 3/08 1.97, Post 3/08 1.97

Sabin C, et al. 21st CROI; Boston, MA; March 3-6, 2014. Abst. 747LB.
Kaiser Cohort: HIV Infection
No Longer a Risk Factor for MI

- Retrospective analysis of Kaiser cohort EMRs during 1996-2011 for inpatient MI diagnosis
- HIV-/HIV+ pts matched 10:1
- MI rates in HIV+ and HIV- converged over time
  - 40% increased risk of MI in HIV+ pts overall, but difference no longer observed in most recent yrs

<table>
<thead>
<tr>
<th>Framingham Risk Score Components, 2010-11</th>
<th>HIV+</th>
<th>HIV-</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Framingham score, 10-yr risk of MI, %</td>
<td>9.2</td>
<td>9.6</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Male, %</td>
<td>90.7</td>
<td>90.4</td>
<td>.42</td>
</tr>
<tr>
<td>Mean age, yrs</td>
<td>47.9</td>
<td>48.5</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>TC &gt; 200 mg/dL, %</td>
<td>30.0</td>
<td>39.6</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>HDL-C &lt; 40 mg/dL, %</td>
<td>39.4</td>
<td>26.2</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Hx of hypertension, %</td>
<td>28.5</td>
<td>26.2</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Hx of smoking, %</td>
<td>48.7</td>
<td>34.9</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

Question

• I routinely check vitamin D levels in my patients.

1. True
2. True, but only if they’re on efavirenz
3. Only if they ask
ACTG 5280: High-Dose Vitamin D and Calcium Attenuate Bone Loss in EFV Pts

- Randomized, double-blind trial in pts initiating TDF/FTC/EFV with baseline vitamin D 10-75 ng/mL
  - Vitamin D3 4000 IU/day plus
  - Calcium carbonate 1000 IU/day
- Significant, 50% reduction in loss of hip BMD at Wk 48 in treated pts
- Smaller nonsignificant difference in spine BMD in treated pts
- Smaller increase in markers of bone turnover in treated pts

![Change in BMD (%)](image)

Decline in BMD From Baseline to Wk 48
- Vitamin D/calcium
- Placebo

CROI 2014: Really Rapid Review

• Elite controllers hospitalized more than HIV patients on treatment [556]
• Rosuvastatin improves lipids, bone density, inflammatory markers but worsens insulin sensitivity [134]
  – 150 subject single site study!
• Risk of NNRTI resistance after treatment interruption 12% [593]
• And finally ...
Acknowledgements and Conflict of Interest

This study has been financed within the framework of the Swiss HIV Cohort Study, supported by the Swiss National Science Foundation (grant # 134277). The study was conducted by the Five Swiss University Hospitals, two Cantonal Hospitals, 15 affiliated hospitals and 36 private physicians listed in http://www.shcs.ch/31-heal.

Conflict of interest: HF grew up in a farm in Zurich “Wyland”, which included a vineyard. His brother produces and sells his own red wine.