CROI 2014: the Treatment Naive Patient

Calvin J. Cohen, MD, MSc
Co PI – New England AETC
Research Director, CRI New England
Harvard Vanguard Medical Associates
Clinical Instructor, Harvard Medical School
Boston, Massachusetts
CROI 2014: “The Retrovirus Conference” the Treatment Naive Patient

Calvin J. Cohen, MD, MSc
Co PI – New England AETC
Research Director, CRI New England
Harvard Vanguard Medical Associates
Clinical Instructor, Harvard Medical School
Boston, Massachusetts
When to Start
Mr. HG is here for a first visit

He is a 22-year-old male living in your city

Known he is HIV positive for just a few months
  - Found out from doing a home test with a new partner

Recent CD4s: ~800 cells/mm³
  - Viral load readings: 5-12,000 c/mL
  - HIV resistance testing – Wild type HIV

Vaccinated for Hep A and B, negative testing for C

Comes to discuss ARV treatment

Not ready to take antiviral meds for the rest of his life
  - Doesn’t fully trust that medications are safe
  - Says he “plays safe only”

What advice do you offer about starting ARVs now?
• A. If you are not ready then it is too soon to start – treatment is “optional”
• B. We should work to get you ready because it is not too soon to start to stay well
• C. Since no 22 year old “plays safe only” – we should discuss treatment for prevention
• D. All of the above
• E. Other
Curing People with HIV: Principles

• **Challenge: Eradicating virus reservoirs**
  - Resting memory CD4 cells have latent but replication competent virus
  - Appear soon after birth
  - Infected soon after exposure

  - Once reservoir present, approach is reactivating latent HIV while on ART, specifically accelerating HIV infected cell death

• **Many challenges remain for cure in adults**
  - Is it possible to accelerate reservoir cell death?
  - Is partial reduction of the reservoir sufficient for a “functional” cure?
### 2014 DHHS Guidelines: Recommendations for Initiation of ART in Naïve Patients

<table>
<thead>
<tr>
<th>Clinical Category</th>
<th>CD4 Cell Count (cells/mm³)</th>
<th>2013 DHHS Guidelines</th>
<th>Strength-Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevention of Transmission</td>
<td>Any value</td>
<td>Treat</td>
<td>AI</td>
</tr>
<tr>
<td>• Perinatal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Heterosexual</td>
<td></td>
<td></td>
<td>AI</td>
</tr>
<tr>
<td>• Other Risks</td>
<td></td>
<td></td>
<td>AIII</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>&lt;350</td>
<td>Treat</td>
<td>AI</td>
</tr>
<tr>
<td></td>
<td>350 to 500</td>
<td>Treat</td>
<td>All</td>
</tr>
<tr>
<td></td>
<td>&gt;500</td>
<td>Treat</td>
<td>BIII</td>
</tr>
</tbody>
</table>

Patients starting ART should be willing and able to commit to treatment and understand the benefits and risks of therapy and the importance of adherence (AIII). Patients may choose to postpone therapy, and providers, on a case-by-case basis, may elect to defer therapy on the basis of clinical and/or psychosocial factors.

Strength of Recommendation: A = Strong; B = Moderate; C = Optional
Quality of Evidence for Recommendation:
I = data from randomized controlled trials;
II = data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes;
III = expert opinion

Available at: http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Revision February 12, 2013
## 2014 EACS Guidelines: When to Start

<table>
<thead>
<tr>
<th>Condition</th>
<th>Current CD4 Lymphocyte Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic HIV infection</td>
<td>Consider</td>
</tr>
<tr>
<td>To Reduce Transmission of HIV</td>
<td>Consider</td>
</tr>
<tr>
<td>Primary HIV infection</td>
<td>Consider</td>
</tr>
<tr>
<td>Symptomatic HIV disease (CDC B or C conditions) including tuberculosis</td>
<td>Recommend</td>
</tr>
<tr>
<td>Conditions (likely or possibly) associated with HIV, other than CDC stage B or C disease:</td>
<td></td>
</tr>
<tr>
<td>HIV-associated neurocognitive impairment</td>
<td>Recommend</td>
</tr>
<tr>
<td>Hodgkin's lymphoma</td>
<td>Recommend</td>
</tr>
<tr>
<td>HPV-associated cancers</td>
<td>Recommend</td>
</tr>
<tr>
<td>High risk for CVD (&gt;20% estimated 10 yr risk) or history of CVD or autoimmune disease, or non-AIDS cancers</td>
<td>Consider</td>
</tr>
</tbody>
</table>
HPTN 052: Treatment as Prevention

Randomized, Placebo-controlled Efficacy and Safety Study
13 Sites in Africa, Asia, Americas

- N=1,763 HIV-positive patients in relationship with HIV-negative partner
- 97% Heterosexual
- CD4 350-550

n=886 immediate HAART
n=1 transmission
96% risk reduction

n=877 Delayed HAART until CD4<250 (or AIDS)
n=27 transmissions

- All received ongoing safe sex education/condoms
- Study stopped four years early by DSMB (May 2011)

Accessed May 12, 2011.
Partner Cohort Study: HIV Transmission Risk Despite Condomless Sex

- International Observational Cohort Study of sero-discordant couples
- Analyzed transmission risk from HIV+ on ARVs with undetectable viral load from condomless sexual acts – no PEP nor PREP used in HIV-
- Analysis of transmissions linked to partner thru phylogenetic analysis

<table>
<thead>
<tr>
<th></th>
<th>Observed Transmissions</th>
<th>95% CI for 100 couple years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>0</td>
<td>0-0.4%</td>
</tr>
<tr>
<td>Anal sex</td>
<td>0</td>
<td>0-0.96%</td>
</tr>
<tr>
<td>Receptive Anal, with or without ejaculation</td>
<td>0</td>
<td>0-1.97%</td>
</tr>
</tbody>
</table>

- **Ten-year risk of HIV Transmission:**
  - 0-3.9% overall
  - 0-9.2% for condomless anal sex

Rodger A, et al. 21st CROI; Boston, MA; March 3-6, 2014. Abst. 153LB.
GSK744 Long Acting Preparation Given as Multiple Doses
q4 Week or q12 Weeks Achieve Plasma Concentrations >4 x PA-IC90 in Healthy Adults

Mean GSK744 plasma concentration-time profiles

- 800mg IM LD, 200mg SC q4w x 3
- 800mg IM LD, 200mg IM q4w x 3
- 800mg IM LD, 400mg IM q4w x 3
- 800mg IM quarterly x 2
- 4* PA-IC 90 (0.664µg/mL)

Spreen W, et al. 7th IAS Conference on HIV Pathogenesis, Treatment and Prevention; June 30-July 3, 2013; Kuala Lumpur, Malaysia Abs WEAB0103

GSK744 5mg/day po Ctau = 0.6 µg/mL
HPTN 052: Primary Events

Number of Subjects Experiencing ≥1 Event

<table>
<thead>
<tr>
<th>Event</th>
<th>Delayed</th>
<th>Immediate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Primary event</td>
<td>77 (9%)</td>
<td>57 (6%)</td>
</tr>
<tr>
<td>AIDS event</td>
<td>61</td>
<td>40</td>
</tr>
<tr>
<td>Deaths</td>
<td>15</td>
<td>11</td>
</tr>
<tr>
<td>Primary event associated</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Deaths from other causes</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Non-AIDS events</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Non-AIDS malignancy</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Cardiovascular/vascular</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Serious liver disease</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>End stage renal disease</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

HR=1.37 (0.97 – 1.93)

Failure Probability

When Will We See the Answer? The START Study

- **ART Naïve HIV-infected individuals**
  Confirmed CD4 count >500 cells/mm³

- **Early ART group**
  Initiate ART immediately following randomization
  N=2,300

- **Deferred ART group**
  Defer ART until the CD4 count declines to <350 cells/mm³ or AIDS develops
  N=2,300

- **Sample Size Increased in 2013 to 4,600 – additional n=600 >35 years old**
  - Enrollment complete - with >4,600 in Dec 2013.

- **Hypothesis: early ART reduces rate of primary endpoint by 28.8%**
  - 43% for AIDS events; 24% for non-AIDS events

www.clinicaltrials.gov
### HPTN 052: Risk Factors for Primary Event

<table>
<thead>
<tr>
<th></th>
<th>Relative Risk</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment Arm (Delayed vs. Immediate)</strong></td>
<td>1.39</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>Baseline (at enrollment) risk factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≥40 (vs. 18-24 yrs)</td>
<td>2.42</td>
<td>0.017</td>
</tr>
<tr>
<td>HIV-1 log(_{10}) RNA (per 1 log higher)</td>
<td>1.34</td>
<td>0.013</td>
</tr>
<tr>
<td>Hemoglobin (grade 2+ vs. 0/1)</td>
<td>2.17</td>
<td>0.025</td>
</tr>
<tr>
<td>Hepatitis B co-infection (yes vs. no)</td>
<td>1.85</td>
<td>0.040</td>
</tr>
<tr>
<td><strong>Time updated risk factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4 (per 50 count higher)</td>
<td>0.90</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Incidence of clinical events significantly lower in immediate ART arm (IRR=0.8, $P=0.02$); difference driven by HIV clinical events (e.g. TB, HSV, VZV, thrush)**

**Factors that were not significant risks for event:**
- Age 25-39
- Gender
- Baseline CD4 count
- HTN
- Active Tb
- use of TMPSMX

Mr. HT and his partner

• HT is your patient
  • Virologically suppressed for years on TDF/FTC/EFV

• He and his HIV- partner JB come in

• They are monogamous – together for a few years
  • They want to enjoy a more intimate sexual life
  • They are sexually “versatile”
  • They prefer sex without condoms “in the way”
  • They’ve been doing so for a few months – and want to know what advice you have
Responses

• A. The data are convincing – condoms are optional for them

• B. Everyone gets to decide their own risk tolerance – up to them

• C. I don’t trust the results – either use condoms and/or consider PrEP

• D. I don’t trust their monogamy – so use condoms to prevent STDs

• E. Get married and stop having sex like normal couples do

• F. Other
What to Start
Mr. EK

- 39-year-old male, moved to your city from Canada
  - Lives with his HIV- partner of several years
  - Initial CD4 count 332 cells/mm³, VL 88,561 c/mL
  - Repeat lab tests 4 months later:
    - CD4 349, VL 77,611 c/mL
    - HIV genotype – Wild type virus
    - Total Chol 244, HDL 35, LDL 159
    - Creat 1.1, eGFR 97, normal glucose
    - Very healthy in general; swims for exercise

- Ready to start ARVs, motivated to protect his partner and himself – he wants your “best” choice for him
  - What regimen is your “best” choice?
Responses

- A. TDF/FTC/EFV
- B. TDF/FTC and ATV/r
- C. TDF/FTC and DRV/r
- D. TDF/FTC and RAL
- E. TDF/FTC/EVG/cob
- F. TDF/FTC and DTG
- G. ABC/3TC and DTG
- H. TDF/FTC/RPV
- I. I don’t have just one best
- J. Other
Which Antiretrovirals: 2014 Currently Available in the US

**NRTIs**
- Abacavir
- Didanosine
- Emtricitabine
- Lamivudine
- Stavudine
- Tenofovir
- Zidovudine

**NNRTIs**
- Delavirdine
- Efavirenz
- Etravirine
- Nevirapine (XR)
- Rilpivirine

**PIs**
- Atazanavir
- Darunavir
- Fos-Amprenavir
- Indinavir
- Lopinavir
- Nelfinavir
- Ritonavir
- Saquinavir
- Tipranavir

**Fusion Inhibitors**
- Enfuvirtide

**Entry Inhibitors**
- Maraviroc

**Integrase Inhibitors**
- Raltegravir
- Elvitegravir*
- Dolutegravir

**PK booster**
- Cobicistat*

*Only available coformulated with TDF/FTC
2014 US DHHS Guidelines: What to Start: Seven Preferred

<table>
<thead>
<tr>
<th>Regimen Type</th>
<th>Preferred Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>NNRTI</td>
<td>EFV/TDF/FTC*</td>
</tr>
<tr>
<td>Boosted PI</td>
<td>ATV/r + TDF/FTC</td>
</tr>
<tr>
<td></td>
<td>DRV/r (once daily) + TDF/FTC</td>
</tr>
<tr>
<td>Integrase Inhibitor</td>
<td>RAL + TDF/FTC</td>
</tr>
<tr>
<td></td>
<td>EVG/cob/TDF/FTC*</td>
</tr>
<tr>
<td></td>
<td>DTG + TDF/FTC</td>
</tr>
<tr>
<td></td>
<td>DTG + ABC/3TC</td>
</tr>
</tbody>
</table>

*Available co-formulated March 2014

One Controversy – ABC and the Risk of MI – the D:A:D cohort

- Analysis of MI risk (n=941 MI) with ABC - pre and post 3/08 in D:A:D
- 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)/100 pt yrs of FU
  - No ABC 0.21 (0.19-0.22)/100 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.
A Second Controversy
Efavirenz – Still a “Gold Standard”?  

• Never surpassed for efficacy

• But...has come in 2nd for tolerability
### STaR
### Adverse Events Leading to Discontinuation of EFV/FTC/FTC through Weeks 48 & 96

<table>
<thead>
<tr>
<th></th>
<th>EFV/FTC/TDF (n=392)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline-Week 48</td>
</tr>
</tbody>
</table>

#### Discontinuations* Due to AE, n (%)
- **Total**: 34 (9%)  +9 (2.3%)

#### AE leading to discontinuation in >1 subject in either arm

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Baseline-Week 48</th>
<th>Week 48-Week 96</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>5 (1.3%)</td>
<td>+1 (0.3%)</td>
</tr>
<tr>
<td><strong>Psychiatric Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal Dreams</td>
<td>4 (1%)</td>
<td>+1 (0.3%)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>3 (0.8%)</td>
<td>+1 (0.3%)</td>
</tr>
<tr>
<td>Depression</td>
<td>7 (1.8%)</td>
<td>+4 (1%)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>2 (0.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Suicidal Ideation</td>
<td>2 (0.5%)</td>
<td>+1 (0.3%)</td>
</tr>
<tr>
<td>Nightmare</td>
<td>2 (0.5%)</td>
<td>0</td>
</tr>
<tr>
<td><strong>GI, General, Skin Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (0.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2 (0.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>2 (0.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Toxic Skin Eruption</td>
<td>2 (0.5%)</td>
<td>0</td>
</tr>
</tbody>
</table>

*Cohen C, et al. EACS Brussels 2013, LBPE7/17*
As-treatment HR 2.16 (1.16-4.00)

Hazard ratio (95% CI) 2.28 (1.27 to 4.10), \( P=0.006 \)

47 events/5,817 PY* (8.08/1,000 PY)

15 events/4,099 PY* (3.66/1,000 PY)

*Person Years, sum of at-risk follow-up

Secondary Analysis: Attempted/Completed Suicide

ITT all follow-up: 27 vs. 7 events, HR 2.6 (1.1 to 5.9, \( P=0.03 \))

As-treated: 14 vs. 5 events, HR 2.3 (0.8 to 6.5, \( P=0.11 \))

ACTG 5257: Comparing Three Preferred Alternatives to EFV
ACTG 5257: Study Design

HIV-infected patients, ≥18 yr, with no previous ART, VL ≥ 1,000 c/mL at U.S. Sites (N=1,809)

Randomized 1:1:1 to Open Label Therapy
Stratified by screening HIV-1 RNA level (≥ vs. <100,000 c/mL), A5260s metabolic substudy participation, cardiovascular risk

ATV 300 mg QD + RTV 100 mg QD + FTC/TDF 200/300 mg QD (N=605)
RAL 400 mg BID + FTC/TDF 200/300 mg QD (N=603)
DRV 800 mg QD + RTV 100 mg QD + FTC/TDF 200/300 mg QD (N=601)

- **Primary Endpoints***
  - Time to HIV-1 RNA >1000 c/mL wk 16 to before wk 24, or >200 c/mL at or after wk 24 (VF)
  - Time to discontinuation of randomized component for toxicity (TF)

- **Pre-planned Composite Endpoint**
  - The earlier occurrence of either VF or TF in a given participant

Landovitz L, et al. 21st CROI; Boston, MA; March 3-6, 2014. Abst. 85.

RTV not provided directly by Study Supply though reimbursed
## ACTG 5257: Failure Comparisons at 96 Weeks

### Virologic Failure

<table>
<thead>
<tr>
<th>Arms</th>
<th>Difference</th>
<th>97.5% CI</th>
<th>Favors</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATV/r vs. RAL</td>
<td>3.4% favors RAL</td>
<td>-0.7%, 7.4%</td>
<td>Equivalent</td>
</tr>
<tr>
<td>DRV/r vs. RAL</td>
<td>5.6% favors RAL</td>
<td>1.3%, 9.9%</td>
<td>Equivalent</td>
</tr>
<tr>
<td>ATV/r vs. DRV/r</td>
<td>-2.2% favors DRV</td>
<td>-6.7%, 2.3%</td>
<td>Equivalent</td>
</tr>
</tbody>
</table>

### Tolerability Failure

<table>
<thead>
<tr>
<th>Arms</th>
<th>Difference</th>
<th>97.5% CI</th>
<th>Favors</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATV/r vs. RAL</td>
<td>13% favors RAL</td>
<td>9.4%, 16%</td>
<td>RAL Superior</td>
</tr>
<tr>
<td>DRV/r vs. RAL</td>
<td>3.6% favors RAL</td>
<td>1.4%, 5.8%</td>
<td>Equivalent</td>
</tr>
<tr>
<td>ATV/r vs. DRV/r</td>
<td>9.2% favors DRV</td>
<td>5.5%, 13%</td>
<td>DRV/r Superior</td>
</tr>
</tbody>
</table>

### Cumulative Failure

<table>
<thead>
<tr>
<th>Arms</th>
<th>Difference</th>
<th>97.5% CI</th>
<th>Favors</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATV/r vs. RAL</td>
<td>15% favors RAL</td>
<td>10%, 20%</td>
<td>RAL Superior</td>
</tr>
<tr>
<td>DRV/r vs. RAL</td>
<td>7.5% favors RAL</td>
<td>3.2%, 12%</td>
<td>RAL Superior</td>
</tr>
<tr>
<td>ATV/r vs. DRV/r</td>
<td>7.5% favors DRV</td>
<td>2.3%, 13%</td>
<td>DRV/r Superior</td>
</tr>
</tbody>
</table>
### ACTG 5257: Toxicity Associated Discontinuation

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>ATV/r (N=605)</th>
<th>RAL (N=603)</th>
<th>DRV/r (N=601)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Toxicity Discontinuation</td>
<td>95 (16%)</td>
<td>8 (1%)</td>
<td>32 (5%)</td>
</tr>
<tr>
<td>Gastrointestinal Toxicity</td>
<td>25</td>
<td>2</td>
<td>14</td>
</tr>
<tr>
<td>Jaundice/Hyperbilirubinemia</td>
<td>47</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other Hepatic Toxicity</td>
<td>4</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Skin Toxicity</td>
<td>7</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Metabolic Toxicity</td>
<td>6</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Renal Toxicity (All Nephrolithiasis)</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Abnormal Chem/Heme (Excl. LFTs)</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Other Toxicity</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

Landovitz L, et al. 21st CROI; Boston, MA; March 3-6, 2014. Abst. 85.
**ACTG 5257: Resistance**

<table>
<thead>
<tr>
<th>ATv/r</th>
<th>RAL</th>
<th>DRV/r</th>
</tr>
</thead>
<tbody>
<tr>
<td>75/94 VF Analyzed</td>
<td>65/85 VF Analyzed</td>
<td>99/115 VF Analyzed</td>
</tr>
</tbody>
</table>

N=9 Any Resistance (12% with VF; 1.5% of ATv/r arm)

- 5 M184V
- 1 K70N + M184V
- 2 T69D/T215A/I/T (1 integrase mutation)

N=18 Any Resistance (27% with VF; 3% of RAL arm)

- 7 M184V
- 1 integrase mutation
- 7 integrase + M184V
- 3 integrase + M184V + K65R

N=4 Any Resistance (4% with VF; <1% of DRV/r arm)

- 3 M184V
- (1 integrase mutation)

Landovitz L, et al. 21st CROI; Boston, MA; March 3-6, 2014. Abst. 85.
ACTG 5257: Lipid Changes at 96 weeks

Fasting LDL-C (mg/dL)
- ATV
- RAL
- DRV

Fasting Triglycerides (mg/dL)
- ATV
- RAL
- DRV

Fasting HDL-C (mg/dL)
- ATV
- RAL
- DRV

Ofotokun I, et al. 21st CROI; Boston, MA; March 3-6, 2014. Abst. 746.
Which Regimen Wins?

- A. TDF/FTC + RAL
- B. TDF/FTC + ATV/r
- C. TDF/FTC + DRV/r
- D. TDF/FTC or ABC/3TC + DTG
- E. TDF/FTC/EVG/cob
- F. TDF/FTC/RPV
- G. Other
- H. Not sure
- I. What do you mean by “wins”?
Can Two-Drug Regimens Replace Three-Drug Regimens?
GARDEL Study: Study Design

Stratified by Screening HIV RNA
(≤ or > 100,000 copies/mL)

ARV-naive patients
≥ 18 years
HIV RNA >1,000 copies/mL
No IAS-USA defined NRTI or PI resistance at screening
HB(s)Ag negative
(N=426)

Week 24
Interim Analysis

Dual Therapy (DT):
LPV/r 400/100 mg BID
+ 3TC 150 mg BID
(n=217)

Triple Therapy (TT):
LPV/r 400/100 mg BID + 3TC or FTC
and a third investigator-selected NRTI in fixed-dose combination (n=209)

Week 48
Primary Endpoint

**GARDEL Study: Primary Efficacy Outcome**

**VL <50 copies/mL (ITTe)**

- **DT**
- **TT**

**Week 48 <50 copies/mL**
- **Observed (n=373)**
- **DT** 95.5%
- **TT** 96.6%
- -1.1%; [-5.6% to 3.4%]

**P=0.777**

---

*Cahn P et al. 14th EACS; Brussels, Belgium; October 16-19, 2013. Abst. LBPS7/6.*
**NEAT 001:**
**DRV/r + RAL vs. DRV/r + TDF/FTC**

- Randomization 1:1 stratified by country and participation in virology/immunology substudy
- 78 sites, 15 European countries
- Composite virological and clinical primary endpoint (6 components)

**Inclusion Criteria:**
- HIV-1 ART-naïve
- ≥18 years
- HIV-1 RNA >1,000 c/mL
- CD4 ≤500/mm³
- HBsAg negative
- No major IAS-USA resistance mutations

**Treatment arms:**
- DRVr 800+100 mg QD + RAL 400 mg BID
- DRV/r 800+100 mg QD + TDF/FTC FDC QD

Minimum Week 96

Raffi F, et al. 21st CROI; Boston, MA; March 3-6, 2014. Abst. 84LB.
### NEAT 001: Primary Endpoint by Baseline Characteristics and Resistance

Raffi F, et al. 21st CROI; Boston, MA; March 3-6, 2014. Abst. 84LB.

<table>
<thead>
<tr>
<th></th>
<th>RAL + DRV/r</th>
<th>TDF/FTC + DRV/r</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong> n = 805</td>
<td>-1.1</td>
<td>8.6</td>
</tr>
<tr>
<td></td>
<td>17.4%</td>
<td>13.7%</td>
</tr>
<tr>
<td><strong>Baseline HIV-1 RNA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 100,000 c/ml n = 530</td>
<td>-3.9</td>
<td>3.5</td>
</tr>
<tr>
<td></td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>≥ 100,000 c/ml n = 275</td>
<td>-0.05</td>
<td>19.3</td>
</tr>
<tr>
<td></td>
<td>36%</td>
<td>27%</td>
</tr>
<tr>
<td></td>
<td><em>P=0.09</em></td>
<td></td>
</tr>
<tr>
<td><strong>Baseline CD4+</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 200/mm³ n = 123</td>
<td>4.7</td>
<td>30.8</td>
</tr>
<tr>
<td></td>
<td>39.0%</td>
<td>21.3%</td>
</tr>
<tr>
<td>≥ 200/mm³ n = 682</td>
<td>-3.4</td>
<td>6.3</td>
</tr>
<tr>
<td></td>
<td>13.6%</td>
<td>12.2%</td>
</tr>
<tr>
<td></td>
<td><em>P=0.02</em></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Genotype Done, n</strong></th>
<th>28/36</th>
<th>13/15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Resistance Mutations, n</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>NRTI</td>
<td>1 (K65R)</td>
<td>0</td>
</tr>
<tr>
<td>PI</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>INI</td>
<td>5 (N155H)*</td>
<td>-</td>
</tr>
</tbody>
</table>