HIV Treatment: What to Start

Joel Gallant, MD, MPH
Johns Hopkins University School of Medicine
Learning Objectives

Upon completion of this presentation, learners should be better able to:

• Assess current guidelines for selection of initial antiretroviral regimens, including the advantages and disadvantages of each

• Appraise the drugs and regimens currently being investigated in phase III clinical trials and their potential role in practice
Off-Label Disclosure

The following off-label/investigational uses will be discussed in this presentation:

- **Investigational agents**: elvitegravir, cobicistat, rilpivirine, S/GSK1349572
- **Investigational coformulations** using investigational and approved agents
Case

• A 30 year old accountant is referred to you by his dentist, who found oral thrush on exam.
• He is found to be HIV+ with a CD4 count of 83 and a viral load of 192,000
• Genotype shows pan-susceptible virus
• He does not have chronic hepatitis B or C. Renal function, liver enzymes, and fasting lipid profile are normal
• He does not use illicit drugs. He has no chronic medical conditions except HTN, well controlled on an ARB
• He says he is ready to start ART. He has no preferences about regimen
Case

• What would you do now?

1. Defer ART until he has seen an adherence counselor and has kept several follow-up appointments
2. Start 2 NRTIs plus EFV
3. Start 2 NRTIs plus a boosted PI
4. Start 2 NRTIs plus RAL
5. Start an NRTI-sparing regimen

<table>
<thead>
<tr>
<th>Preferred Agents for First-Line Therapy (AI recommendations)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTIs</td>
</tr>
<tr>
<td>Plus a third agent</td>
</tr>
<tr>
<td>NNRTI</td>
</tr>
<tr>
<td>Boosted PI</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>INSTI</td>
</tr>
</tbody>
</table>

Other regimens categories (DHHS)

- Alternative (BI)
- Acceptable (CI)
- Acceptable but more definitive data are needed (CIII)
- May be acceptable but should be used with caution (CI-III)
- Not recommended
Choosing the Initial Regimen: The 4 Questions

- EFV, a boosted PI, or RAL?
- If a boosted PI, which one?
- Which NRTI backbone?
- Something else?
Question 1: EFV vs. PI/r vs. RAL?

<table>
<thead>
<tr>
<th></th>
<th>PROS</th>
<th>CONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFV</td>
<td>• Gold standard for virologic efficacy</td>
<td>• CNS side effects</td>
</tr>
<tr>
<td></td>
<td>• Easiest regimens (1-2 pills/d)</td>
<td>• Teratogenicity</td>
</tr>
<tr>
<td></td>
<td>• Minimal long-term toxicity</td>
<td>• Genetic barrier: resistance with interruption</td>
</tr>
<tr>
<td></td>
<td>• PK forgiving of missed doses</td>
<td>• Poorer CD4 response than with other classes</td>
</tr>
</tbody>
</table>
**Question 1: EFV vs. PI/r vs. RAL?**

<table>
<thead>
<tr>
<th></th>
<th>PROS</th>
<th>CONS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EFV</strong></td>
<td>• Gold standard for virologic efficacy</td>
<td>• CNS side effects</td>
</tr>
<tr>
<td></td>
<td>• Easiest regimens (1-2 pills/d)</td>
<td>• Teratogenicity</td>
</tr>
<tr>
<td></td>
<td>• Minimal long-term toxicity</td>
<td>• Genetic barrier: resistance with interruption</td>
</tr>
<tr>
<td></td>
<td>• PK forgiving of missed doses</td>
<td>• Poorer CD4 response than with other classes</td>
</tr>
<tr>
<td><strong>PI/r</strong></td>
<td>• As effective as EFV (ATV/r in ACTG 5202)</td>
<td>• Greater pill burden</td>
</tr>
<tr>
<td></td>
<td>• Less resistance with failure</td>
<td>• GI side effects</td>
</tr>
<tr>
<td></td>
<td>• Preferred in pregnancy</td>
<td></td>
</tr>
</tbody>
</table>
### Question 1: EFV vs. PI/r vs. RAL?

<table>
<thead>
<tr>
<th></th>
<th>PROS</th>
<th>CONS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EFV</strong></td>
<td>• Gold standard for virologic efficacy</td>
<td>• CNS side effects</td>
</tr>
<tr>
<td></td>
<td>• Easiest regimens (1-2 pills/d)</td>
<td>• Teratogenicity</td>
</tr>
<tr>
<td></td>
<td>• Minimal long-term toxicity</td>
<td>• Genetic barrier: resistance with interruption</td>
</tr>
<tr>
<td></td>
<td>• PK forgiving of missed doses</td>
<td>• Poorer CD4 response than with other classes</td>
</tr>
<tr>
<td><strong>PI/r</strong></td>
<td>• As effective as EFV (ATV/r in ACTG 5202)</td>
<td>• Greater pill burden</td>
</tr>
<tr>
<td></td>
<td>• Less resistance with failure</td>
<td>• GI side effects</td>
</tr>
<tr>
<td></td>
<td>• Preferred in pregnancy</td>
<td></td>
</tr>
<tr>
<td><strong>RAL</strong></td>
<td>• As effective as EFV with better tolerability (STARTMRK)</td>
<td>• No long-term data</td>
</tr>
<tr>
<td></td>
<td>• Lipid neutral (vs. EFV, PI/r)</td>
<td>• Twice-daily dosing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Resistance risk similar to EFV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Expensive</td>
</tr>
</tbody>
</table>
Case

• The patient wants a once-daily regimen and says he can’t afford the time to adjust to EFV side effects. What do you choose?

1. 2 NRTIs + LPV/r
2. 2 NRTIs + DRV/r
3. 2 NRTIs + ATV/r
4. Convince him to take EFV
5. 2 NRTIs plus once-daily RAL
Question 2: Which Boosted PI?

<table>
<thead>
<tr>
<th>PI/r</th>
<th>PROS</th>
<th>CONS</th>
</tr>
</thead>
</table>
| ATV/r | • Superior to LPV/r at 96 wks (CASTLE)  
• Lowest pill burden (2/d) | • Gastric acid requirement  
• Food requirement  
• Jaundice & scleral icterus |
## Question 2: Which Boosted PI?

<table>
<thead>
<tr>
<th>PI/r</th>
<th>PROS</th>
<th>CONS</th>
</tr>
</thead>
</table>
| ATV/r | • Superior to LPV/r at 96 wks (CASTLE)  
• Lowest pill burden (2/d) | • Gastric acid requirement  
• Food requirement  
• Jaundice & scleral icterus |
| DRV/r | • Superior to LPV/r (VL>100K, ARTEMIS)  
• Better tolerability and less hyperlipidemia (vs. LPV/r)  
• No gastric acid issues (vs. ATV/r) | • Food requirement  
• Rash |
### Question 2: Which Boosted PI?

<table>
<thead>
<tr>
<th>PI/r</th>
<th>PROS</th>
<th>CONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATV/r</td>
<td>• Superior to LPV/r at 96 wks (CASTLE)</td>
<td>• Gastric acid requirement</td>
</tr>
<tr>
<td></td>
<td>• Lowest pill burden (2/d)</td>
<td>• Food requirement</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Jaundice &amp; scleral icterus</td>
</tr>
<tr>
<td>DRV/r</td>
<td>• Superior to LPV/r (VL&gt;100K, ARTEMIS)</td>
<td>• Food requirement</td>
</tr>
<tr>
<td></td>
<td>• Better tolerability and less hyperlipidemia (vs. LPV/r)</td>
<td>• Rash</td>
</tr>
<tr>
<td></td>
<td>• No gastric acid issues (vs. ATV/r)</td>
<td></td>
</tr>
<tr>
<td>LPV/r</td>
<td>• Coformulated</td>
<td>• Requires 200 mg/d of RTV</td>
</tr>
<tr>
<td></td>
<td>• No food restrictions</td>
<td>• Metabolic toxicity</td>
</tr>
<tr>
<td></td>
<td>• Preferred for pregnancy</td>
<td>• GI side effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Risk of MI in D:A:D</td>
</tr>
</tbody>
</table>
### Question 2: Which Boosted PI?

<table>
<thead>
<tr>
<th>PI/r</th>
<th>PROS</th>
<th>CONS</th>
</tr>
</thead>
</table>
| ATV/r | • Superior to LPV/r at 96 wks (CASTLE)  
• Lowest pill burden (2/d) | • Gastric acid requirement  
• Food requirement  
• Jaundice & scleral icterus |
| DRV/r | • Superior to LPV/r (VL>100K, ARTEMIS)  
• Better tolerability and less hyperlipidemia (vs. LPV/r)  
• No gastric acid issues (vs. ATV/r) | • Food requirement  
• Rash |
| LPV/r | • Coformulated  
• No food restrictions  
• Preferred for pregnancy  
• Least expensive | • Requires 200 mg/d of RTV  
• Metabolic toxicity  
• GI side effects  
• Risk of MI in D:A:D |
| FPV/r | • No food restrictions | • 700/100 mg BID dose: no advantage over LPV/r  
• 1400/100 mg QD dose: not as well studied as other PI/r options |
Case

• Which NRTI backbone do you choose?

1. TDF/FTC
2. ABC/3TC (after HLA B*5701 testing)
3. AZT/3TC
4. I would use an NRTI-sparing regimen
**Question 3: Which NRTI Backbone?**

<table>
<thead>
<tr>
<th>NRTIs</th>
<th>PROS</th>
<th>CONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF/FTC</td>
<td>• Best backbone with EFV</td>
<td>• Renal toxicity</td>
</tr>
<tr>
<td></td>
<td>• Only studied backbone with RAL</td>
<td>• Possible increased risk with PIs</td>
</tr>
<tr>
<td></td>
<td>• Preferred for HBV coinfection</td>
<td>• Bone density?</td>
</tr>
</tbody>
</table>

- RAL: Raltegravir
### Question 3: Which NRTI Backbone?

<table>
<thead>
<tr>
<th>NRTIs</th>
<th>PROS</th>
<th>CONS</th>
</tr>
</thead>
</table>
| **TDF/FTC** | • Best backbone with EFV  
  • Only studied backbone with RAL  
  • Preferred for HBV coinfection | • Renal toxicity  
  • Possible increased risk with PIs  
  • Bone density? |
| **ABC/3TC** | • Lack of renal toxicity | • Need for HLA B*5701 screening to avoid ABC HSR  
  • Inferior to TDF/FTC with VL >100,000  
  • Increased risk of MI?  
  • ACTG 5202 safety/tolerability data |
Abacavir and Cardiovascular Risk

- Conflicting data from multiple cohort studies and clinical trials

- If there is an increased risk:
  - it is greatest in patients with multiple cardiovascular risk factors
  - pathogenesis unknown, but not due to metabolic factors
    - Inflammation, endothelial function, platelet reactivity/function?

- Cardiovascular risk of untreated HIV probably greater than risk of any specific drug

Tenofovir and Renal Risk

- TDF can cause two types of nephrotoxicity:
  - **Glomerular**: decreased kidney function
  - **Tubular**: Fanconi’s syndrome, phosphate wasting

- Low risk, especially with initial therapy or when combined with EFV

- Boosted PIs increase tenofovir levels and may increase nephrotoxicity, though incidence has been low in trials of 1st line therapy

- Tubular toxicity not detected by creatinine alone. Look for glycosuria, proteinuria, phosphate wasting
Which NRTI Backbone?

TDF/FTC

Kidney disease

HLA B*5701 negative, VL <100,000, low CV risk

ABC/3TC
Which NRTI Backbone?

TDF/FTC

HLA B*5701 positive, high CV risk, (VL>100,000?)

Kidney disease

NRTI-sparing regimen?

ABC/3TC
ACTG 5202: ABC/3TC vs. TDF/FTC
Primary Virologic Endpoint
(High VL Stratum at DSMB Action)

N=797; median (25th, 75th) follow-up = 60 weeks (28, 84)


Log rank test p-value = 0.0003
HR (95% CI) 2.33 (1.46, 3.72)
**PROGRESS: LPV/r + RAL vs LPV/r + NRTIs in ART-Naive Patients**

- Randomized, open-label, multicenter phase III trial in ART-naive pts with VL> 1000
  - LPV/r 400/100 mg BID + RAL 400 mg BID (n = 101) vs
  - LPV/r 400/100 mg BID + TDF/FTC (n = 105)
- Relatively low mean baseline VL: 4.25 log_{10}

- Similar CD4 gain at Wk 48
  - LPV/r + RAL: 215
  - LPV/r + NRTIs: 245

Potential New First-Line Options

- CCR5 inhibitor-containing regimens
- “Quad”: elvitegravir/cobicistat/TDF/FTC
- Cobicistat as PI booster, including possible coformulations
- Dolutegravir (including coformulation with ABC/3TC)
- Rilpivirine, including coformulation with TDF/FTC
## What about maraviroc?

<table>
<thead>
<tr>
<th>PROS</th>
<th>CONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>MVC</td>
<td></td>
</tr>
</tbody>
</table>
| • R5 virus more likely with early/initial therapy  
  • Very well tolerated  
  • Greater CD4 count than with EFV  
  • High barrier to resistance | • No long-term data  
  • Twice-daily dosing  
  • Studied only with ZDV/3TC  
  • Requires baseline tropism testing  
  • Complex dosing |
15% of patients reclassified from R5 to D/M at screening when retested with enhanced sensitivity phenotypic tropism assay

- Noninferiority criteria (rates of HIV-1 RNA < 50 copies/mL) met when D/M patients excluded

Determination of Viral Tropism

- Phenotypic assay used in clinical trials involving CCR5 antagonists to determine viral tropism\[^{1,2}\]

- Genotyping of env V3 loop may be an alternative to phenotyping\[^{3,4}\]
  - Less costly and faster, though some assays inferior to phenotypic assay\[^{5}\]

- Genotypic\[^{6}\] and phenotypic\[^{7}\] assays available for determining tropism from PBMC proviral DNA

Potential New Options

- CCR5 inhibitor-containing regimens
- “Quad”: elvitegravir/cobicistat/TDF/FTC
- Cobicistat as PI booster, including possible coformulations
- Dolutegravir (including coformulation with ABC/3TC)
- Rilpivirine, including coformulation with TDF/FTC
Cobicistat-Boosted EVG + FTC/TDF vs. EFV/FTC/TDF in Naive Pts: Phase II trial

- Cobicistat (GS-9350, COB): investigational CYP3A inhibitor (boosting agent)

- Elvitegravir (EVG): investigational integrase inhibitor

**ART-naive pts with CD4 ≥50, VL ≥5000, no NRTI, NNRTI or PI resistance (N = 71)**

**Wk 24 primary endpoint analysis**

**Wk 24 stratum-weighted difference: +5% (95% CI: -11.0% to 21.1%)**

**HIV-1 RNA < 50 c/mL (%)**

Potential New Options

- CCR5 inhibitor-containing regimens
- “Quad”: elvitegravir/cobicistat/TDF/FTC
- Cobicistat as PI booster, including possible coformulations
- Dolutegravir (including coformulation with ABC/3TC)
- Rilpivirine, including coformulation with TDF/FTC
Cobicistat-Boosted ATV Virologic Efficacy Similar to ATV/r in Naive Pts

- Phase II study comparing cobicistat (GS-9350) vs RTV as boosting agent for atazanavir

**Graph Details:**
- **ART-naive pts with CD4 ≥50, VL ≥5000, no NRTI, NNRTI or PI resistance (N = 79)**
- **Wk 24 stratum-weighted difference:** -1.9% (95% CI: -18.4% to 14.7%)
- **Wk 48**

**Graph Symbols:**
- **COB–Boosted ATV + FTC/TDF (n = 50)**
- **RTV-Boosted ATV + FTC/TDF (n = 29)**

**Graph Notes:**
Cobicistat: AEs When Combined With EVG/FTC/TDF or ATV/r + TDF/FTC

<table>
<thead>
<tr>
<th>AEs, n (%)</th>
<th>EVG/COB/TDF /FTC (n = 48)</th>
<th>EFV/FTC/TDF (n = 23)</th>
<th>COB + ATV + FTC/TDF (n = 50)</th>
<th>RTV + ATV TDF/FTC (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1-4 AEs related to randomized drug</td>
<td>17 (35)</td>
<td>13 (57)</td>
<td>10 (20)</td>
<td>7 (24)</td>
</tr>
<tr>
<td>Abnormal dreams, nightmares</td>
<td>5 (10)</td>
<td>8 (35)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0</td>
<td>3 (13)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4 (8)</td>
<td>3 (13)</td>
<td>1 (2)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>2 (4)</td>
<td>2 (9)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4 (8)</td>
<td>1 (4)</td>
<td>3 (6)</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (4)</td>
<td>1 (4)</td>
<td>5 (10)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Bilirubin, total</td>
<td>0</td>
<td>0</td>
<td>40/49 (82)</td>
<td>25 (86)</td>
</tr>
<tr>
<td>Creatinine (grade 1)</td>
<td>1 (2)</td>
<td>0</td>
<td>6 (12)</td>
<td>0</td>
</tr>
<tr>
<td>Δ mean serum creatinine from BL to Wk 24, mg/dL</td>
<td>+ 0.14</td>
<td>+ 0.04</td>
<td>+ 0.18</td>
<td>+ 0.14</td>
</tr>
<tr>
<td>Δ mean eGFR from BL to Wk 24, mL/min</td>
<td>- 18</td>
<td>- 7</td>
<td>- 15</td>
<td>- 14</td>
</tr>
</tbody>
</table>

Potential New Options

- CCR5 inhibitor-containing regimens
- “Quad”: elvitegravir/cobicistat/TDF/FTC
- Cobicistat as PI booster, including possible coformulations
- Dolutegravir (including coformulation with ABC/3TC)
- Rilpivirine, including coformulation with TDF/FTC
SPRING-1: Virologic Response to S/GSK1349572 vs EFV at Wk 16

- CD4 count increases 153-176 on 572 vs 116 on EFV
- No serious adverse events related to 572

50-mg dose chosen for phase III trial

Time to VL < 50 shorter for 572 than EFV ($P < .001$ for each comparison)

Potential New Options

- CCR5 inhibitor-containing regimens
- “Quad”: elvitegravir/cobicistat/TDF/FTC
- Cobicistat as PI booster, including possible coformulations
- Dolutegravir (including coformulation with ABC/3TC)
- Rilpivirine, including coformulation with TDF/FTC
ECHO, THRIVE: Rilpivirine vs EFV in Treatment-Naive Patients

VL < 50 (ITT-TLOVR) at Wk 48

*P < .0001 for noninferiority at -12% margin.

ECHO, THRIVE: Treatment Failure, Resistance, and Adverse Events

### Treatment Failure in ECHO and THRIVE

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>RPV</th>
<th>EFV</th>
</tr>
</thead>
<tbody>
<tr>
<td>VF</td>
<td>9.0</td>
<td>4.8</td>
</tr>
<tr>
<td>AE</td>
<td>6.7</td>
<td>2.0</td>
</tr>
</tbody>
</table>

### Resistance at Virologic Failure

**Wk 48 Outcome**

<table>
<thead>
<tr>
<th></th>
<th>Rilpivirine (n = 686)</th>
<th>Efavirenz (n = 682)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VF with resistance data, n</td>
<td>62</td>
<td>28</td>
</tr>
<tr>
<td>No NNRTI or NRTI RAMs,%</td>
<td>29</td>
<td>43</td>
</tr>
<tr>
<td>≥ 1 Emergent NNRTI RAM,%</td>
<td>63</td>
<td>54</td>
</tr>
<tr>
<td>Most frequent NNRTI RAM</td>
<td>E138K</td>
<td>K103N</td>
</tr>
<tr>
<td>≥ 1 Emergent NRTI RAMs, %</td>
<td>68</td>
<td>32</td>
</tr>
<tr>
<td>Most frequent NRTI RAM</td>
<td>M184I</td>
<td>M184V</td>
</tr>
</tbody>
</table>

### Adverse Events and Discontinuation

<table>
<thead>
<tr>
<th></th>
<th>Rilpivirine (n = 686)</th>
<th>Efavirenz (n = 682)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DC for AE</td>
<td>3</td>
<td>8</td>
<td>.0005</td>
</tr>
<tr>
<td>Most Common AEs of Interest, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any neurologic AE</td>
<td>17</td>
<td>38</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Any psychiatric AE</td>
<td>15</td>
<td>23</td>
<td>.0002</td>
</tr>
<tr>
<td>Any rash</td>
<td>3</td>
<td>14</td>
<td>&lt; .0001</td>
</tr>
</tbody>
</table>

Predictions (and questions) involving the future

- There will soon be new options for initial therapy
  - TDF/FTC/RPV?
    - Better tolerability, but efficacy and resistance concerns
  - “Quad”?  
    - Phase III studies in progress. Concern about creatinine elevation
  - Dolutegravir + ABC/3TC coformulation  
    - Attractive 1st agent, but depends on what happens with earlier entries
    - Use of ABC/3TC

- Boosted PIs will remain the best choice for patients with unreliable adherence
  - Will cobicistat replace ritonavir?
Predictions (and questions) involving the future

- **Generics: the wild card:**
  - Generic 3TC, EFV, SQV coming
  - For the first time, preferred agents will be available as generics
  - Will 3rd party payers notice?
  - Will coformulations no longer be covered?
  - Will the bar be higher for development of new first-line agents?
    - Need to show superior efficacy and/or safety rather than non-inferiority and improved convenience