Learning Objectives

After attending this presentation, learners will be able to:

• Describe appropriate options for initial antiretroviral regimens in selected patient populations;
• Identify and manage multiclass antiretroviral failure with currently available drugs;
• Describe available data on antiretroviral drugs and strategies in development.
Overview

- Options for first line ART
- Managing multiclass failure in 2013
- Drugs in the pipeline

Case 1

- JS is a 45 yo woman with HIV
- Recently diagnosed during routine screening offered by her primary care MD
- Viral load 54,000 copies/ml
- CD4 450 cells/mm3
- Ready to start ART
- PMH
  - FH CHD (Mother died of an MI at the age of 50)
  - HTN well controlled on medication
  - Serum creatinine 1.1-1.3 past few years, no proteinuria
  - Fasting lipids, LDL 120 mg/dl, HDL 40 mg/dl, TG 120 mg/dl
- She does not smoke, rare alcohol use and no history of drug use

Choice of Initial Regimen

Tenofavir/emtricitabine (TDF/FTC) OR
Abacavir/lamivudine (ABC/3TC)

WITH

Third agent (NNRTI, boosted PI, or InSTI):
  - Efavirenz OR
  - Atazanavir OR
  - Darunavir OR
  - Raltegravir

### Alternative Initial Antiretroviral Regimens*

<table>
<thead>
<tr>
<th>Component</th>
<th>Alternative Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>NNRTI plus nRTIs</td>
<td>- Nevirapine plus tenofovir/emtricitabine or abacavir/lamivudine (Bla)</td>
</tr>
<tr>
<td></td>
<td>- Rilpivirine/tenofovir/emtricitabine (or rilpivirine plus abacavir/lamivudine) with</td>
</tr>
<tr>
<td></td>
<td>baseline plasma HIV-1 RNA &lt; 100,000 copies/mL (Bla)</td>
</tr>
<tr>
<td>PI/r plus nRTIs</td>
<td>- Darunavir/r plus abacavir/lamivudine (BIII)</td>
</tr>
<tr>
<td></td>
<td>- Lopinavir/r plus tenofovir (Bla) (or abacavir/lamivudine) (Bla)</td>
</tr>
<tr>
<td>InSTI plus nRTIs</td>
<td>- Raltegravir plus abacavir/lamivudine (BIIa)</td>
</tr>
<tr>
<td></td>
<td>- Elvitegravir/cobicistat/tenofovir/emtricitabine (BIIb)</td>
</tr>
</tbody>
</table>

* See comment  

### What would you prefer as a first line ART regimen for this patient?

1. 2 NRTI + efavirenz or rilpivirine
2. 2 NRTI + atazanavir/r or darunavir
3. 2 NRTI + raltegravir
4. Elvitegravir/cobicistat/TDF/FTC
5. Something else

### ECHO, THRIVE: Rilpivirine vs EFV in ART-Naïve Patients

- Randomized, double-blind phase III trials

- ECHO (N = 690)
  - Treatment-naïve
  - VL < 5000
  - no NNRTI RAMs
  - susceptible to NRTIs

- THRIVE (N = 678)
  - Treatment-naïve
  - VL < 5000
  - no NNRTI RAMs
  - susceptible to NRTIs

- RPV + TDF/FTC (n = 346)
- EFV + TDF/FTC (n = 344)
- RPV 25 mg QD + 2 NRTIs† (n = 340)
- EFV + 2 NRTIs† (n = 339)

†THRIVE only  
*Selected by investigator from ABC/3TC, TDF/FTC, ZDV/3TC.


EIHA, THRIVE: Rilpivirine vs EFV in ART-Naïve Patients

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†THRIVE only  
*Selected by investigator from ABC/3TC, TDF/FTC, ZDV/3TC.

ECHO/THRIIVE: Viral Load <50, 96 Week ITT-TLOVR Data

- More virologic failures (VF) with RPV vs. EFV: 14% vs. 7.6%
  - Difference due to more VF between Wks 0-48; VF similar Wks 48-96
  - NRTI mutations more common with VF on RPV vs. EFV
  - Cross-resistance to ETR more common with RPV failures (E138K mutation)
- D/C due to AE more common with EFV vs. RPV: 8.5% vs. 4.1%


EVG/COBI/TDF/FTC: “Alternative” First-line Regimen

- EVG/COBI/TDF/FTC recommended as “alternative” regimen in treatment-naive patients with ClCr > 70 mL/min (BI12-13)
- Benefits
  - Noninferior to EFV/TDF/FTC, [14,15] ATV/RTV + TDF/FTC[16]
  - 1-tablet, once-daily dosing
- Limitations
  - Potential for drug–drug interactions
  - Limited safety data; limited data in advanced disease, women
  - Possible increased risk proximal renal tubulopathy
  - Food requirement


SPRING 2: 2 NRTI + [DTG vs. RAL]

Study population: Rx-naive (N=822)

Treatment difference +3% (95% CI -2.2%, +7.1%)
- exludes -10% (non-inferiority threshold)
  ⇒ DTG is non-inferior to RAL
ABC/3TC + DTG vs. TDF/FTC/EFV

Rx-naïve patients (N=822)

Week 48 difference in response +7.4% (95% CI: +2.5% to +12.3%; p=0.003); excludes -10% threshold

→ DTG regimen superior to EFV regimen

Is there a role for NRTI sparing regimens in first line ART?

1. Yes
2. No

Novel Combinations: NRTI-sparing regimens

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>Efficacy/Resistance</th>
<th>Lipids</th>
<th>Renal</th>
<th>Bone</th>
<th>Bilirubin</th>
</tr>
</thead>
<tbody>
<tr>
<td>AS042</td>
<td>LPV/r + EFV</td>
<td>Neutral</td>
<td>Elevated</td>
<td>Neutral</td>
<td>Neutral</td>
<td>-</td>
</tr>
<tr>
<td>PROGRESS</td>
<td>LPV/r + RAL</td>
<td>Neutral</td>
<td>Elevated</td>
<td>Neutral</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CCTG389</td>
<td>LPV/r + RAL</td>
<td>Neutral</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SPARTAN</td>
<td>ATV + RAL</td>
<td>More Resistance</td>
<td>Neutral</td>
<td>-</td>
<td>-</td>
<td>Elevated</td>
</tr>
<tr>
<td>MVC Manufacturer</td>
<td>ATV/r + MVC</td>
<td>Neutral</td>
<td>-</td>
<td>-</td>
<td>Elevated</td>
<td>-</td>
</tr>
<tr>
<td>MONET</td>
<td>DRV/r</td>
<td>Not Non-Inferior</td>
<td>Elevated</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>AS250</td>
<td>DRV/r + RAL</td>
<td>Inferior</td>
<td>TBD</td>
<td>TBD</td>
<td>TBD</td>
<td>TBD</td>
</tr>
</tbody>
</table>

NRTI-sparing regimens: X + PI/r

- EFV + LPV/r (96 weeks) Riddler NEJM 2008
- RAL + LPV/r (96 weeks) Reynes AIDS Res Hum Retro 2013
- RAL + ATV (24 weeks) Kozal HIV Clin Trials 2013
- RAL + DRV/r
  - ACTG 5262 (48 weeks; N=112, single arm) Taiwo AIDS 2011
  - NEAT-001 (96 weeks; N=800, compared to TDF/FTC + DRV/r)
- MVC + ATV/r (96 weeks) Mills JAIDS 2013
- MVC + DRV/r (MIDAS, 48 weeks) Taiwo IAS 2012 #TUPE099

Let’s vote again: What would you prefer as a first line ART regimen for this patient?

1. 2 NRTI + efavirenz
2. 2 NRTI + rilpivirine
3. 2 NRTI + atazanavir/r
4. 2 NRTI + darunavir
5. 2 NRTI + raltegravir
6. Fixed dose integrase combination with elvitegravir/cobicistat/TDF/FTC
7. Something else

ACTG 5303: Immunologic, Renal, Bone and CNS Outcomes of an NRTI Sparing Initial Regimen

- Treatment naive without HBV infection
- No baseline resistance to DRV and CCR5 tropism
  - Arm A: DRV/r 800/100 mg + MVC 150 mg + FTC 200 mg + TDF placebo QD
  - Arm B: DRV/r 800/100 mg + TDF 300 mg + FTC 200 mg + MVC placebo QD
Case 2

- 48 year old man with longstanding HIV
- Extensive treatment experience, but clinically stable
- Recently moved to Atlanta and comes to see you for management
- Brings the following records to his visit

Dx with HIV in 1989
- CD4 350-500 range until mid 1990s
- Treated with ZDV then ddI, then ZDV/3TC
- Added IDV in 1997
- Later changed to ABC/3TC/EFV in 2003
- Problems with adherence to care and treatment
- Changed to tenofovir/FTC/ ZDV / lopinavir/rit 2 years ago
- Most recent labs CD4 now 75, VL 69,000

Most recent phenotype/genotype
Lopinavir/rit, FTC/tenofovir and zidovudine

<table>
<thead>
<tr>
<th>DRUG</th>
<th>Susceptibility</th>
<th>Percent of HIV isolates</th>
<th>NET ASSESSMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lopinavir</td>
<td>rit</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>ABC</td>
<td>N</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>FTC</td>
<td>N</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>N</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Zidovudine</td>
<td></td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Nevirapine</td>
<td></td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Efavirenz</td>
<td></td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Atazanavir</td>
<td></td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Darunavir</td>
<td></td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Dolutegravir</td>
<td></td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Raltegravir</td>
<td></td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Maraviroc</td>
<td></td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Rilpivirine</td>
<td></td>
<td>0%</td>
<td>0%</td>
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<td>Tivicay</td>
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<td>0%</td>
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<td></td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Most current resistance pattern analysis:
- Lopinavir/rit, FTC/tenofovir and zidovudine
Would you also send an HIV-1 co-receptor tropism assay?

1. Yes
2. No
Tropism test returns R5 Tropism

## Available Antiretroviral Agents

### Nucleoside RTIs
- Zidovudine (ZDV)
- Didanosine (ddI)
- Zalcitabine (ddC)
- Lamivudine (3TC)
- Abacavir (ABC)
- Emtricitabine (FTC)

### Nonnucleos(t)ide RTIs
- Nevirapine (NVP)
- Delavirdine (DLV)
- Efavirenz (EFV)
- Etravirine (ETR)
- Tenofovir DF (TDF)

### Protease Inhibitors
- Saquinavir (SQV)
- Ritonavir (RTV)
- Indinavir (IDV)
- Nelfinavir (NFV)
- Amprenavir (APV)
- Tornadivir (LPV/r)
- Atazanavir (ATV)
- Fosamprenavir (Fos-APV)
- Tipranavir (TPV)
- Darunavir (DRV)

### Boosters
- Ritonavir (RTV)
- Cobicistat* (cobi)

### Integrase Inhibitors
- Raltegravir (RAL)
- Eviroligravir (ETG)
- Daliligravir*

### Fusion Inhibitor
- Enfuvirtide (T-20)

### CCR5 Antagonist
- Maraviroc (MVC)

### In expanded access or submitted for regulatory approval

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## Available Antiretroviral Agents For Our Patient

### Nucleoside RTIs
- Emtricitabine (FTC)

### Nonnucleos(t)ide RTIs
- Etravirine (ETR)

### Protease Inhibitors
- Darunavir (DRV)

### Integrase Inhibitors
- Raltegravir (RAL)
- Elvitegravir (ETG)

### Fusion Inhibitor
- Enfuvirtide (T-20)

### CCR5 Antagonist
- Maraviroc (MVC)

* In expanded access or submitted for regulatory approval

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March 2013
As you consider options for the next regimen would you include NRTIs?

1. Yes
2. No

ACTG OPTIONS Study Hypothesis

- Omitting NRTIs would be non-inferior to adding NRTIs in treatment experienced subjects starting a new optimized regimen in the setting of triple class resistance.

OPTIONS Study Design

- Multi-center, US-based
- Individually designed regimen:Study regimen with cPSS > 2; and selection of 2-3 NRTIs
- 20 potential 3-4 drug combinations combining the following drugs:
  - DRV/r
  - ENF
  - ETR
  - MVC
  - RAL
  - TPV/r

- Open-label randomization
- Add NRTIs to potent study regimen
- Primary endpoint: 1 year
dpoint: 2 years
- Addition of 2-3 NRTIs

Tashima K, et al CROI 2013 LB
OPTIONS Study Endpoints

- **Primary efficacy endpoint**
  - Regimen failure defined as a composite of first of confirmed virologic failure or discontinuation of NRTI assignment

- **Primary safety endpoint**
  - Time to initial episode of severe sign/symptom or lab value prior to discontinuation of NRTI assignment

- **Non-inferiority threshold**: rule out that omitting NRTIs had 15% higher probability of regimen failure through 1 year compared to adding NRTIs

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Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Omit NRTIs N=179</th>
<th>Add NRTIs N=181</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>46</td>
<td>46</td>
</tr>
<tr>
<td>Male</td>
<td>74%</td>
<td>75%</td>
</tr>
<tr>
<td>Race: Black, non-Hispanic</td>
<td>39%</td>
<td>44%</td>
</tr>
<tr>
<td>Ethnicity: Hispanic</td>
<td>26%</td>
<td>21%</td>
</tr>
<tr>
<td>CD4 (cells/mm³)</td>
<td>212</td>
<td>193</td>
</tr>
<tr>
<td>Plasma HIV RNA (log₁₀ copies/mL)</td>
<td>4.2</td>
<td>4.2</td>
</tr>
<tr>
<td>Years on ARVs</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>R₅-only tropism</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>Prior Enfuvirtide (ENF) or Integrase-inhibitor use</td>
<td>18%</td>
<td>19%</td>
</tr>
<tr>
<td>cPSS of study treatment regimen</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

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Chosen regimen and NRTI combinations

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Add NRTIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAL+DRV/r+ETR</td>
<td>TDF+FTC (RTI)</td>
</tr>
<tr>
<td>RAL+DRV/r+ETR+MVC</td>
<td>2TC+TDF+FTC (RTI)</td>
</tr>
<tr>
<td>RAL+FTI+MPC</td>
<td>Other</td>
</tr>
<tr>
<td>RAL+DRV/r+ETR+ENF</td>
<td>Other</td>
</tr>
</tbody>
</table>

Randomization

- **OMIT NRTIs**: 56%
- **Add NRTIs**: 44%
Omitting NRTIs is NOT Inferior to Adding NRTIs to an Optimized Regimen

**Primary Efficacy Outcome Comparisons**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Omit NRTIs (N=179)</th>
<th>Add NRTIs (N=181)</th>
<th>Omitting NRTIs not inferior to adding NRTIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regimen Failure</td>
<td>53 (50%)</td>
<td>48 (26%)</td>
<td>9.2 (6.1, 12.5)</td>
</tr>
<tr>
<td>Virologic Failure</td>
<td>44 (25%)</td>
<td>45 (25%)</td>
<td>0.4 (9.4, 8.7)</td>
</tr>
<tr>
<td>Step NRTI assignment</td>
<td>15 (8%)</td>
<td>10 (6%)</td>
<td>3.6 (1.7, 9.0)</td>
</tr>
</tbody>
</table>

Only 5 persons (1.4%) censored for regimen failure outcome. 90% had at least 42 weeks exposure to NRTIs.

**Summary of Findings Options Study**

- Regimen failure was not more likely among those omitting NRTIs versus adding NRTIs to an optimized new regimen.
- HIV RNA, CD4 cell responses were similar.
- Fewer deaths in the Omit NRTI arm.
- No statistically significant difference in primary safety when considering both symptoms and labs.

**Available Antiretroviral Agents For Our Patient**

- **Nucleoside RTIs**
  - Tenofovir (TDF)
  - Emtricitabine (FTC)
- **Nonnucleoside RTIs**
  - Etravirine (ETV)
  - Delavirdine (DLV)
- **Protease Inhibitors**
  - Maraviroc (MVC)
  - Raltegravir (RAL)
  - Elvitegravir (ETG)
- **Integrase Inhibitors**
  - Raltegravir (RAL)
  - Elvitegravir (ETG)
- **Fusion Inhibitor**
  - Enfuvirtide (T-20)
- **CCR5 Antagonist**
  - Maraviroc (MVC)

* In expanded access or submitted for regulatory approval.

March 2013
Which regimen would you select for this patient?

1. RAL + DRV/r + Etravirine
2. RAL + DRV/r + Maraviroc
3. Elvitegravir/FTC/TDF/ Cobi + DRV
4. Elvitegravir/FTC/TDF/ Cobi + MVC
5. DRV/r + TDF/FTC + Maraviroc QD
6. Something else

Case 3

- 45 year old M from Peru
- Past medical history:
  - HIV/AIDS-Diagnosed 1993
  - OIs-shingles, thrush
- Previous regimens:
  - 2000-2002 3TC-didanosine-rit-indinavir
  - 2002-2004 3TC-didanosine-lopinavir and ritonavir
  - 2004-2006 EFV-SQV-lopinavir and ritonavir
  - 2006-2010 3TC-TDF TMC114-rit
  - 2010-2011 RAL-enfuvirtide-ETR
  - 2/2011-5/12 TDF + FTC
- CD4 27 cells/mm3, VL 123,000

- Genotype: 10/27/2011
- RT: E44D, D67N, T69D, V75M, V179E, Y181C, Y188L
- HIV-1 co-receptor tropism: R5
How would you manage this patient?

1. MVC + ETV + DRV/r
2. Wait for DTG + MVC + DRV/r
3. T20 + MVC + DRV/r
4. Something else

DTG for INSTI-Resistance

- DTG active in vitro against molecular clones with RAL- and EVG-resistance mutations

Kobayashi AAC 2011;55:813

- VIKING 1: Phase 2b study of subjects with genotypic RAL-resistance (N=50)
  - Study rx: DTG 50 mg qd or bid X 10d, then OBR
  - Day 10: 78% (qd) + 96% (bid) had VL >0.7 logi or <<400
  - Week 24: 41% (qd) + 75% (bid) had VL <50
Viking-3: DTG for Integrase Inh-Experienced Pts  
Study population: Resistant to 2 classes + RAL or EVG, VL >500 (N=183)  

- Day 8 VL Δ:  
  -1.43 log_{10} copies/mL,  
P<0.001  
- ITT-E, N=183  

Overall, 63% were fully suppressed at Week 24 by Snapshot algorithm  

Percentage of subjects with VL<50 copies/mL  

Viking-3: Day 8 Responses by Baseline Resistance  

<table>
<thead>
<tr>
<th>Primary INI-resistance mutations at BL</th>
<th>N</th>
<th>Mean HIV-1 RNA (log_{10}) change from BL (SD) at Day 8</th>
<th>% &gt;1-log_{10} HIV-1 RNA decline or &lt;50 copies/mL at Day 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>183</td>
<td>-1.4 (0.61)</td>
<td>82%</td>
</tr>
<tr>
<td>No primary mutations</td>
<td>60</td>
<td>-1.6 (0.55)</td>
<td>95%</td>
</tr>
<tr>
<td>Y143</td>
<td>28</td>
<td>-1.7 (0.42)</td>
<td>96%</td>
</tr>
<tr>
<td>N155</td>
<td>33</td>
<td>-1.4 (0.50)</td>
<td>82%</td>
</tr>
<tr>
<td>Q148 + ≤ 1 Secondary mutation*</td>
<td>32</td>
<td>-1.1 (0.50)</td>
<td>69%</td>
</tr>
<tr>
<td>Q148 + ≥ 2 Secondary mutations*</td>
<td>21</td>
<td>-1.0 (0.81)</td>
<td>48%</td>
</tr>
</tbody>
</table>

*Key secondary mutations were G140A/C/S, L74I, and E138A/K/T  

Nichols Glasgow 2012 #O232

GSK 1265744 ('744)  
- Integrase inhibitor similar to DTG; similar resistance  
- 2.25 log cps/ml ↓ in HIV+ individuals (5+30 mg oral)  
- Nanotechnology formulation; SC + IM injections  
- T ½ 21-50 days!  
- Supports monthly or quarterly dosing  
- Safety: ISR and nodules with SC dosing  

Nichols Glasgow 2012 #O232
How would you manage this patient

1. Wait for DTG + MVC + DRV/r

Summary

- Expanding options for first line ART allow clinicians to tailor regimens to patient characteristics
  - One size does not fit all
  - Increased focus on long term safety and efficacy
- Nucleosides do not add to third line ART when at least 2 other active drugs available and may enhance toxicity
- Pipeline of new drugs is limited