Update on Antiretroviral Treatment Guidelines 2015

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Learning Objectives

• Identify recent changes in guidelines regarding initial therapy of HIV infection

• Apply the most recent guidelines regarding monitoring of patients on antiretroviral therapy

• Utilize the latest guideline-recommended practices for diagnosing and treating special populations, including those with HCV infection, HIV-2 infection
Case Scenario # 1

• 55 yo African-American F with GERD, allergic rhinitis, newly diagnosed with HIV
• CD4 count 150, HIV RNA 250,000
• Nurse. Irregular meal-times
• Medications: omeprazole, fluticasone
• Estimated GFR 60. HLA-B5701 negative

• She is interested in starting therapy
Which regimen would you start?

A. Dolutegravir/ABC/3TC
B. Dolutegravir + TDF/FTC
C. EFV/TDF/FTC
D. RPV/TDF/FTC
E. EVG/cobi/TDF/FTC
F. DRV/r + TDF/FTC
G. RAL + TDF/FTC
Case Scenario # 2

- 55 yo white M with newly diagnosed HIV
- History of hypertension, depression
- Good adherence with medications (lisinopril, paroxetine). Smokes 1 ppd. Regular meals
- Exam: obese man. BP 130/80
- CD4 count 550. HIV RNA 16,000
- Estimated GFR 65. Lipids: TC 210. LDL 160
- HLA-B5701 negative
- He says he’s interested in treatment with a single-pill combination
You would start which regimen?

A. Dolutegravir/ABC/3TC
B. Dolutegravir + TDF/FTC
C. EFV/TDF/FTC
D. RPV/TDF/FTC
E. EVG/cobi/TDF/FTC
F. DRV/r + TDF/FTC
G. RAL + TDF/FTC
Updated: April 8, 2015

Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

Developed by the HHS Panel on Antiretroviral Guidelines for Adults and Adolescents – A Working Group of the Office of AIDS Research Advisory Council (OARAC)

http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf
What’s New in the Guidelines?

• New recommendations regarding “What to Start”, including case-based scenarios to guide selection
• Expanded section on management of virologic failure, including isolated CNS rebound
• New section on “Poor CD4 cell recovery and persistent inflammation despite viral suppression”
• Acute/early HIV section updated with new CDC diagnostic testing algorithm
• New information summarizing interactions between antiretroviral medications and HCV therapy
• Updated section on HIV-2 infection
What to Start

http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf
## Recommended Regimens (n=10)

| NNRTI (n=3) | EFV/TDF/FTC  
|            | RPV/TDF/FTC*§ 
|            | EFV + ABC/3TC* |
| PI (n=3)   | ATV/r + TDF/FTC  
|            | ATV/r + ABC/3TC* 
|            | DRV/r + TDF/FTC |
| INSTI (n=4) | DTG + ABC/3TC  
|            | DTG + TDF/FTC  
|            | EVG/cobi/TDF/FTC  
|            | RAL +TDF/FTC |

*Only for patients with VL <100K. §Only for patients with CD4 >200
Main Changes in “What to Start”

1. EFV/TDF/FTC moved to Alternative
2. ATV/r + TDF/FTC moved to Alternative
3. Regimens previously recommended only for pts with VL <100,000 moved to Alternative or Other: RPV/TDF/FTC, ATV/r or EFV +ABC/3TC
4. DRV/r + RAL and LPV/r + 3TC included among Other regimens but only for patients who cannot take TDF or ABC
5. ATV/cobi and DRV/cobi included among Alternative regimen options
6. Case scenarios table added to help guide selection
## What to Start – 2015

### Recommended Regimens (n=5)

<p>| | |</p>
<table>
<thead>
<tr>
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</thead>
</table>
| **INSTI (n=4)** | DTG/ABC/3TC  
| | DTG + TDF/FTC  
| | EVG/cobi/TDF/FTC  
| | RAL +TDF/FTC  
| **PI (n=1)** | DRV/r + TDF/FTC |

[http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf](http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf)
## Alternative Regimens

<table>
<thead>
<tr>
<th>NNRTI (n=2)</th>
<th>EFV/TDF/FTC RPV/TDF/FTC*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI (n=3)</td>
<td>ATV/r or cobi§ + TDF/FTC</td>
</tr>
<tr>
<td></td>
<td>DRV/cobi§ + TDF/FTC</td>
</tr>
<tr>
<td></td>
<td>DRV/r or cobi + ABC/3TC</td>
</tr>
</tbody>
</table>

*Only if VL <100K and >200. §Only if Cr Cl >70

Effective and tolerable but have potential disadvantages, have limitations for use in certain patient populations, or have less supporting data than Recommended Regimens

An alternative regimen may be the preferred regimen for some patients
Change 1: EFV/TDF/FTC Moved to Alternative

- EFV: long track record of safety and effectiveness but, compared with new regimens, decreased tolerability, mostly because of CNS side effects
  - DTG + ABC/3TC superior to EFV/TDF/FTC, largely because of more treatment discontinuations in EFV group (10% vs. 2%)
  - More tolerability failures with EFV than RPV

Walmsley S et al, NEJM, 2013
Efavirenz and Suicidality

- In retrospective analysis of multiple ACTG studies, increased suicidality in those randomized to EFV-containing regimens as compared to EFV-free regimens.

Mollan K et al, Ann Int Med, 2014
Change 2: ATV/r + TDF/FTC Moved to Alternative

ACTG A5257

HIV+ adults, no previous ART (n=1809)

Randomized 1:1:1. Open Label Therapy

ATV/r + FTC/TDF  RAL + FTC/TDF  DRV/r + FTC/TDF

RAL superior to both PI/r regimens for combined tolerability and virologic efficacy; DRV/r superior to ATV/r

• All 3 regimens had equivalent virologic efficacy
• ATV/r less well tolerated than DRV/r or RAL (mainly because of hyperbilirubinemia/jaundice)

Tolerability failure:
ATV/r: 14%
RAL: 1%
DRV/r: 5%

• Other ATV drawbacks: absorption impaired by acid-lowering therapy; kidney- and gall-stones
• Intriguing association between ATV/r use and slower progression of carotid IMT (ACTG A5260s), but no known clinical advantage

Change 3: Regimens Recommended Only for Patients with VL <100,000 Moved

- Regimens with decreased potency in patients with VL >100K: ABC/3TC + EFV or ATV/r (ACTG 5202)\(^1\); RPV/TDF/FTC\(^2\)

- RPV/TDF/FTC moved to Alternative
- ABC/3TC + EFV or ATV/r moved to Other

Wk 96 VL <50

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Week 96 VL &lt;50</th>
</tr>
</thead>
<tbody>
<tr>
<td>RPV + 2 NRTI*</td>
<td>78%</td>
</tr>
<tr>
<td>EFV + 2 NRTI*</td>
<td>78%</td>
</tr>
</tbody>
</table>

VL >100 K, CD4<200: more virologic failures with RPV

NRTI-limiting Regimens for Patients who cannot take TDF or ABC

- DRV/r + RAL (NEAT001)\(^1\) or LPV/r + 3TC (GARDEL)\(^2\)

- DRV/r + RAL non-inferior to DRV/r + TDF/FTC overall but among those with:
  - CD4 count <200: DRV/r + RAL inferior to DRV/r + 2 NRTI
  - VL >100 K: More failures in NRTI-sparing group

- LPV/r + 3TC non-inferior to LPV/r + 2 NRTI
  - LPV/r + 3TC: greater pill burden and potential toxicities than other 1\(^{\text{st}}\) line regimens

Choosing An Initial Regimen

- EFV
  - RPV
  - EVG/cobi
  - EFV
  - EVG/cobi
  - ATV/r
  - DRV/r
  - ATV/r

- DTG
  - RAL
  - DTG
  - EFV
  - DTG
  - DRV/r
  - RAL
  - ATV/r
Choosing an Antiretroviral Regimen:
Two decisions

• **Step 1**: Decide which NRTIs to use

• **Step 2**: Decide which drug to use within the NNRTI, PI or INSTI class
<table>
<thead>
<tr>
<th>NRTI</th>
<th>PROS</th>
<th>CONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF/FTC</td>
<td>• Single pill options available (with EFV, RPV, EVG/cobi)</td>
<td>• Nephrotoxicity (particularly in those receiving other nephrotoxic agents, PIs)</td>
</tr>
<tr>
<td></td>
<td>• Active vs. HBV</td>
<td>• Increased loss of bone mineral density</td>
</tr>
<tr>
<td></td>
<td>• Lowers lipids</td>
<td></td>
</tr>
<tr>
<td>ABC/3TC</td>
<td>• Not nephrotoxic</td>
<td>• Must confirm HLA-B5701 negative</td>
</tr>
<tr>
<td></td>
<td>• Coformulated with DTG and 3TC</td>
<td>• Some studies, but not all, show association with MI</td>
</tr>
</tbody>
</table>

http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf
# Choosing Between NRTIs

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Preferred Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-B5701+</td>
<td>TDF (cannot use ABC)</td>
</tr>
<tr>
<td>Kidney Disease</td>
<td>ABC</td>
</tr>
<tr>
<td>High cardiac risk</td>
<td>Favor TDF</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>Favor TDF</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>Favor ABC</td>
</tr>
<tr>
<td>Pre-ART VL &gt;100 K</td>
<td>If using with EFV or ATV/r → TDF/FTC</td>
</tr>
<tr>
<td>HBV</td>
<td>TDF/FTC or TDF/3TC</td>
</tr>
</tbody>
</table>

http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf
## Choosing Between INSTI, NNRTI, PI: Pre-ART Characteristics

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Consideration</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 &lt; 200</td>
<td>Because of higher rates of virologic failure, do not use:</td>
</tr>
<tr>
<td></td>
<td>• RPV-based regimens</td>
</tr>
<tr>
<td></td>
<td>• DRV/r + RAL</td>
</tr>
<tr>
<td>HIV RNA &gt; 100K</td>
<td>Do not use the following regimens:</td>
</tr>
<tr>
<td></td>
<td>• RPV-based regimens</td>
</tr>
<tr>
<td></td>
<td>• ABC/3TC with EFV or ATV/r</td>
</tr>
<tr>
<td></td>
<td>• DRV/r + RAL</td>
</tr>
<tr>
<td>Must treat before drug resistance results</td>
<td>Avoid NNRTI-based regimen. Consider using PI (DRV/r)</td>
</tr>
<tr>
<td>known</td>
<td></td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Scenario</th>
<th>Consideration</th>
</tr>
</thead>
<tbody>
<tr>
<td>One pill once daily regimen desired</td>
<td>Options include:</td>
</tr>
<tr>
<td></td>
<td>• DTG/ABC/3TC</td>
</tr>
<tr>
<td></td>
<td>• EFV/TDF/FTC</td>
</tr>
<tr>
<td></td>
<td>• EVG/c/TDF/FTC</td>
</tr>
<tr>
<td></td>
<td>• RPV/TDF/FTC (if VL &lt;100 K, CD4 &gt;200)</td>
</tr>
<tr>
<td>Food effects</td>
<td>Take with food:</td>
</tr>
<tr>
<td></td>
<td>• Boosted ATV or DRV</td>
</tr>
<tr>
<td></td>
<td>• EVG/c/TDF/FTC</td>
</tr>
<tr>
<td></td>
<td>• RPV/TDF/FTC (at least 390 cal)</td>
</tr>
<tr>
<td></td>
<td>Take on empty stomach:</td>
</tr>
<tr>
<td></td>
<td>• EFV-based regimens</td>
</tr>
</tbody>
</table>

[Source](http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf)
## Presence of Other Conditions

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Consideration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychiatric illnesses</td>
<td>Consider avoiding EFV</td>
</tr>
<tr>
<td>Acid-lowering therapy</td>
<td>Caution with RPV, ATV</td>
</tr>
<tr>
<td>Concomitant CYP3A4 metabolized medication</td>
<td>Avoid or caution with PIs, cobi</td>
</tr>
<tr>
<td>Polyvalent cation (Al, Ca, Mg, Fe, Zn)</td>
<td>Caution with INSTI (reduced absorption)</td>
</tr>
<tr>
<td>Metformin</td>
<td>Caution with DTG</td>
</tr>
</tbody>
</table>

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Monitoring Patient on ART
Monitoring after Starting ART

- Chemistries, BUN/Cr, LFTs: wk 2-8, then every 3-6 mo.
- CBC/diff: every 3-6 mo.
- Fasting glucose or HbA1c: every 3-6 mo. if previously abnormal; every 12 mo. if normal
- Lipids: if abnormal, every 6 mo; normal: every 12 mo.
- U/A every 12 months (every 6 mo. if on tenofovir)
  - Tenofovir → Fanconi’s syndrome: glucosuria, proteinuria (≥1+), urinary phosphate wasting
  - Cobicistat, dolutegravir inhibit creatinine secretion → ↑ serum Cr without affecting renal function
    - If >0.4 mg/dL increase in Cr on cobi → check for TDF toxicity

<table>
<thead>
<tr>
<th>Clinical Scenario</th>
<th>VL Monitoring</th>
<th>CD4 Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>First 2 yrs of ART</td>
<td>Every 3 to 4 mo.</td>
<td>Every 3 to 6 mo.</td>
</tr>
<tr>
<td>After 2 yrs of ART, VL suppressed, CD4 300-500</td>
<td>Can extend to every 6 mo.</td>
<td>Every 12 mo.</td>
</tr>
<tr>
<td>After 2 yrs of ART, VL suppressed, CD4 &gt;500</td>
<td></td>
<td>Optional</td>
</tr>
<tr>
<td>Change in clinical status, e.g. new HIV clinical sx or drug that may affect CD4 count</td>
<td>Every 3 mo.</td>
<td>Perform CD4 count, repeat as clinically indicated</td>
</tr>
</tbody>
</table>

http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf
Persistently low CD4 cell counts (<200) despite viral suppression associated with increased mortality and non-AIDS morbidity

Adding ARV to a suppressive regimen does not improve CD4 cell recovery, and is not recommended

Persistent immune activation and inflammation may independently mediate risk of mortality and non-AIDS morbidity -- but specific interventions unproven

Focus should be on healthy lifestyle, smoking cessation, managing HTN, dyslipidemia, DM

http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf
Special Populations: HCV

- Check www.hcvguidelines.org for when and what to start

“This website is constantly being updated. Please remember to always refresh your page.”
Interactions between HIV and HCV Drugs

• Ledipasvir/sofosbuvir
  – TDF: levels increased; monitor for toxicity
  – ABC: OK
  – EFV: monitor for TDF toxicity b/o increased levels
  – RPV: OK
  – If PI/r or PI/c used with TDF, consider alternative HCV therapy; if coadministered, close monitoring
  – RAL, DTG OK. Avoid EVG/cobi/TDF/FTC
Interactions between HIV and HCV Drugs

- Ombitasvir/Paritaprevir/Ritonavir + Dasabuvir
  - NRTI, including TDF: OK
  - Avoid all NNRTI
  - Only HIV PI that is OK: ATV
    - 300 mg at same time as 3D regimen
    - Discontinue RTV or cobi in HIV regimen while on HCV therapy
  - RAL OK, DTG likely OK. Avoid EVG/cobi/TDF/FTC
• HIV-2 should be considered in persons of West African origin or in those with sexual exposure to persons from that area
• Diagnosis: HIV-1/2 Ab differentiation assay
• HIV-2 RNA testing now available through U. Washington and NY State Dept. of Health
• HIV-2: resistant to NNRTI, enfuvirtide
• Therapy should be with 2 NRTI + INSTI or HIV-2 active boosted PI (DRV, LPV, SQV)
Case Scenario # 1

• 55 yo F with newly diagnosed HIV
• Salient considerations
  – GERD, requiring proton-pump inhibitor (affects RPV, ATV/r)
  – Allergic rhinitis, on nasal fluticasone (interacts with PI, cobi)
  – Low CD4 count (150), high VL (250,000) – avoid RPV
  – Irregular meal-times (nurse)
  – Estimated GFR 60
  – HLA-B5701 negative
Which regimen would you start?

A. Dolutegravir/ABC/3TC
B. Dolutegravir + TDF/FTC
C. EFV/TDF/FTC
D. RPV/TDF/FTC
E. EVG/cobi/TDF/FTC
F. DRV/r + TDF/FTC
G. RAL + TDF/FTC
Case Scenario # 2

• 55 yo white M with newly diagnosed HIV
• Salient considerations:
  – High risk for cardiovascular disease (HTN, smoking)
    • 2013 AHA risk calculator: 10 yr ASCVD risk is 13%
  – Low VL (16,000), high CD4 count (550)
  – Estimated CrCl 65 (cobi with TDF only recommended if CrCl >70)
  – Borderline lipids (favors TDF)
  – Regular meals
  – Prefers single-pill combination
You would start which regimen?

A. Dolutegravir/ABC/3TC
B. Dolutegravir + TDF/FTC
C. EFV/TDF/FTC
D. RPV/TDF/FTC
E. EVG/cobi/TDF/FTC
F. DRV/r + TDF/FTC
G. RAL + TDF/FTC