Disclosures

- Relevant Financial Disclosures
  None

- Non-FDA Approved Uses
  None
Objectives

- Describe fundamentals of antiretroviral therapy (ART)
  - Identify HIV antiretroviral drugs by mechanism/class, names, and coformulations
  - Summarize current treatment guidelines for initiating ART (or at least know where to find them)
How do we characterize ART?

- **Potency:**
  - How effective suppressing HIV replication?
  - \( \log \) HIV RNA decline, \( \% \) patients **suppressed** at a certain time period, rapidity of decline, duration of response
  - PI, NNRTI, integrase inhibitors > potency than NRTI
  - Usually potency is more of an issue in salvage regimens
How do we characterize ART?

- **Adverse Events (AEs):**
  - Short- and long-term AEs
  - Co-morbidities play a role in long term AEs
  - May be related to drug-drug interactions
How do we characterize ART?

• **Tolerability:**
  
  – Short-term side effects
  
  – Dosing requirements, pill size & burden, route
  
  – Patient (pill size) or medication (AEs) related
How do we characterize ART?

• **Resistance:**
  
  – Stay tuned...
Retrovirus Life Cycle

Nucleos(t)ide RTI
TDF; TAF; ABC; 3TC; FTC; ZDV; ddI; d4T

Entry Inhibitors
Nucleoside RTI
Integrate Inhibitors
Non-Nucleoside RTI
Protease Inhibitors

HIV
HIV RNA
HIV DNA
Nucleus
Genomic RNA
mRNA
Gag
Myr
Gag-Pol

Host Cell
CD4
CCR5
CXCR4

www.nwaetc.org
Nucleos(t)ide Reverse Transcriptase Inhibitor (NRTI)

- Lamivudine (Epivir® 3TC)
- Emtricitabine (Emtriva® FTC)
- Abacavir (Ziagen® ABC)
- Tenofovir diisopropyl fumarate (Viread® TDF)
- Tenofovir alafenamide (TAF - see coformulations)

- Zidovudine (Retrovir® AZT)
- Didanosine (Videx EC® ddI)
- Stavudine (Zerit® d4T)
NRTI Adverse Effects

• Class Effects
  – Nausea (mild)
  – Mitochondrial toxicity (historical interest?)

• ABC
  – Hypersensitivity
  – HLA-B*5701 mediated (NPV 100%)

• TDF
  – Renal toxicity
  – Tubulopathy; Fanconi’s syndrome
  – TAF avoids this (↓[plasma] ↑[cellular])
Retrovirus Life Cycle

Nucleoside RTI
- TDF; TAF; ABC; 3TC; FTC; ZDV; ddI; d4T

Non-Nucleoside RTI
- EFV; NVP
- etravirine (ETR)
- rilpivirine (RPV)

www.nwaetc.org
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)

- Efavirenz (Sustiva® EFV)
- Etravirine (Intelence® ETR)
- Rilpivirine (Edurant® RPV)
- Nevirapine (Viramune® NVP)
- Delavirdine (Rescriptor® DLV)
NNRTI Adverse Effects

• Class Effects
  – Rash (including Stevens-Johnson syndrome)
  – Hepatotoxicity

• EFV
  – Neuropsychiatric: abnormal dreams, dizziness, impaired concentration
  – Pregnancy risk
  – Dyslipidemia
  – Suicidality

• ETR & RPV
  – Rash (including SJS)

Low resistance threshold
Retrovirus Life Cycle

Nucleoside RTI
- TDF
- TAF
- ABC
- 3TC
- FTC
- ZDV
- ddI
- d4T

Protease Inhibitors
- ATV
- DRV
- LPVr
- FPV
- SQV
- IDV
- RTV
- NFV
- TPV

Non-Nucleoside RTI
- EFV
- NVP
- etravirine (ETR)
- rilpivirine (RPV)

Entry Inhibitors
- CCR5
- CD4
- CXCR4

Integrase Inhibitors

Non-Nucleoside RTI

Protease Inhibitors

Host Cell

Nucleus

HIV RNA

HIV DNA

genomic RNA

mRNA

Myr

Gag-Pol

Gag

www.nwaetc.org
Protease Inhibitors (PI)

- Darunavir (Prezista® DRV)
- Atazanavir (Reyataz® ATV)
- Ritonavir (Norvir® RTV, r) – boosting only
- [Cobicistat (Tybost® COBI, c) – boosting only]
- Fosamprenavir (Lexiva® FPV)
- Lopinavir + Ritonavir (Kaletra® LPVr)

- Indinavir (Crixivan® IDV)
- Nelfinavir (Viracept® NFV)
- Saquinavir (Invirase® SQV)
- Tipranavir (Aptivus® TPV)
- Amprenavir (Agenerase® APV)
PI Adverse Effects

• Class Effects:
  – Diarrhea (most boosted PI, RTV dose is key)
  – Nausea
  – Metabolic
    • Fat deposition - lipodystrophy/lipohypertrophy
      – Abdomen, buffalo hump
    • Increased cholesterol and/or triglycerides
      – Less with ATV, DRV
    • Insulin resistance
  – Darunavir (and TPV, FPV) – sulfa-related rash
  – Hepatotoxicity: TPV and DRV > others?
  – Cobicistat: increased Cr
  – Atazanavir (and indinavir)
    • Increased bilirubin (possible jaundice)
    • Kidney stones

*High resistance threshold*
Retrovirus Life Cycle

Nucleoside RTI
- TDF; TAF; ABC; 3TC; FTC; ZDV; ddI; d4T

Integrase Inhibitors
- raltegravir (RAL)
- elvitegravir (EVG)
- dolutegravir (DTG)

Entry Inhibitors

Nucleoside RTI

Integrase Inhibitors

Protease Inhibitors
- ATV; DRV; LPVr; FPV; SQV; IDV; RTV; NFV; TPV

Non-Nucleoside RTI
- EFV; NVP
- etravirine (ETR)
- rilpivirine (RPV)

www.nwaetc.org
Integrase Strand Transfer Inhibitors (INSTI)

- Raltegravir (Isentress® RAL)
- Elvitegravir (Vitekta® EVG) – coformulated in Stribild® and Genvoya®
- Dolutegravir (Tivicay® DTG) – coformulated in Triumeq®
Retrovirus Life Cycle

**Entry Inhibitors**
enfuvirtide (ENF; T20)  
maraviroc (MVC)

**Nucleoside RTI**
TDF; TAF; ABC; 3TC;  
FTC; ZDV; ddi; d4T

**Integrase Inhibitors**
raltegravir (RAL)  
elvitegravir (EVG)  
dolutegravir (DTG)

**Protease Inhibitors**
ATV; DRV; LPVr; FPV; SQV;  
IDV; RTV; NFV; TPV

**Non-Nucleoside RTI**
EFV; NVP  
etravirine (ETR)  
rilpivirine (RPV)

www.nwaetc.org
ART Co-formulations

- Epzicom® ABC/3TC
- Truvada® TDF/FTC
- Descovy® TAF/FTC
- Atripla® EFV/TDF/FTC
- Complera® RPV/TDF/FTC
- Odefsey® RPV/TAF/FTC
- Stribild® EVGc/TDF/FTC
- Genvoya® EVGc/TAF/FTC
- Triumeq® DTG/ABC/3TC
- Prezincobix® DRVc
- Evotaz® ATVc
- Combivir® AZT/3TC
- Trizivir® AZT/ABC/3TC
Panel on Antiretroviral Guidelines for Adults and Adolescents.
Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents.
Department of Health and Human Services.
Available at http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf.
DHHS evidence ratings

- **Recommendations**
  - A. Strong
  - B. Moderate
  - C. Optional

- **Evidence**
  - I. RCT
  - II. Observational studies
  - III. Expert opinion
When to start?

**Initiation of Antiretroviral Therapy** *(Last updated January 28, 2016; last reviewed January 28, 2016)*

<table>
<thead>
<tr>
<th>Panel’s Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Antiretroviral therapy (ART) is recommended for all HIV-infected individuals, regardless of CD4 T lymphocyte cell count, to reduce the morbidity and mortality associated with HIV infection (AI).</td>
</tr>
<tr>
<td>- ART is also recommended for HIV-infected individuals to prevent HIV transmission (AI).</td>
</tr>
<tr>
<td>- When initiating ART, it is important to educate patients regarding the benefits and considerations regarding ART, and to address strategies to optimize adherence. On a case-by-case basis, ART may be deferred because of clinical and/or psychosocial factors, but therapy should be initiated as soon as possible.</td>
</tr>
</tbody>
</table>

Panel on Antiretroviral Guidelines for Adults and Adolescents.
Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents.
Department of Health and Human Services.
Available at http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf.
Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection

The INSIGHT START Study Group*
Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection

The INSIGHT START Study Group*

A  Time to First Primary Event

<table>
<thead>
<tr>
<th>Month</th>
<th>Immediate initiation</th>
<th>Deferred initiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2326</td>
<td>2359</td>
</tr>
<tr>
<td>6</td>
<td>2302</td>
<td>2326</td>
</tr>
<tr>
<td>12</td>
<td>2279</td>
<td>2281</td>
</tr>
<tr>
<td>18</td>
<td>2163</td>
<td>2135</td>
</tr>
<tr>
<td>24</td>
<td>1801</td>
<td>1803</td>
</tr>
<tr>
<td>30</td>
<td>1437</td>
<td>1417</td>
</tr>
<tr>
<td>36</td>
<td>1031</td>
<td>1021</td>
</tr>
<tr>
<td>42</td>
<td>757</td>
<td>729</td>
</tr>
<tr>
<td>48</td>
<td>541</td>
<td>520</td>
</tr>
<tr>
<td>54</td>
<td>336</td>
<td>334</td>
</tr>
<tr>
<td>60</td>
<td>110</td>
<td>103</td>
</tr>
</tbody>
</table>

No. at Risk

Estimated Percentage

Immediate initiation

Estimated Percentage

Deferred initiation

DOI: 10.1056/NEJMoa1506816
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# Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection

**The INSIGHT START Study Group**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Percentage in Group</th>
<th>Immediate Initiation</th>
<th>Deferral Initiation</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤35 yr</td>
<td>48.8</td>
<td>15 (0.43)</td>
<td>31 (0.91)</td>
<td></td>
<td>0.47</td>
</tr>
<tr>
<td>&gt;35 yr</td>
<td>51.2</td>
<td>27 (0.78)</td>
<td>65 (1.85)</td>
<td></td>
<td>0.42</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>73.2</td>
<td>35 (0.66)</td>
<td>74 (1.40)</td>
<td></td>
<td>0.47</td>
</tr>
<tr>
<td>Female</td>
<td>26.8</td>
<td>7 (0.42)</td>
<td>22 (1.34)</td>
<td></td>
<td>0.31</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>30.1</td>
<td>15 (0.82)</td>
<td>28 (1.52)</td>
<td></td>
<td>0.57</td>
</tr>
<tr>
<td>White</td>
<td>44.5</td>
<td>21 (0.63)</td>
<td>53 (1.54)</td>
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<td>0.40</td>
</tr>
<tr>
<td>Other</td>
<td>25.4</td>
<td>6 (0.34)</td>
<td>15 (0.91)</td>
<td></td>
<td>0.37</td>
</tr>
<tr>
<td>Geographic region</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High income</td>
<td>46.0</td>
<td>20 (0.56)</td>
<td>51 (1.42)</td>
<td></td>
<td>0.39</td>
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<tr>
<td>Low or moderate income</td>
<td>54.0</td>
<td>22 (0.65)</td>
<td>45 (1.35)</td>
<td></td>
<td>0.48</td>
</tr>
<tr>
<td>Baseline CD4+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;600 cells/mm³</td>
<td>31.5</td>
<td>10 (0.44)</td>
<td>35 (1.54)</td>
<td></td>
<td>0.28</td>
</tr>
<tr>
<td>600–800 cells/mm³</td>
<td>48.6</td>
<td>24 (0.70)</td>
<td>46 (1.38)</td>
<td></td>
<td>0.50</td>
</tr>
<tr>
<td>&gt;800 cells/mm³</td>
<td>19.9</td>
<td>8 (0.63)</td>
<td>15 (1.14)</td>
<td></td>
<td>0.56</td>
</tr>
<tr>
<td>Baseline HIV RNA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5000 copies/ml</td>
<td>31.8</td>
<td>12 (0.56)</td>
<td>18 (0.83)</td>
<td></td>
<td>0.66</td>
</tr>
<tr>
<td>5000–30,000 copies/ml</td>
<td>35.5</td>
<td>13 (0.53)</td>
<td>36 (1.41)</td>
<td></td>
<td>0.38</td>
</tr>
<tr>
<td>&gt;30,000 copies/ml</td>
<td>32.5</td>
<td>17 (0.72)</td>
<td>42 (1.92)</td>
<td></td>
<td>0.37</td>
</tr>
<tr>
<td>Smoker</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>31.9</td>
<td>18 (0.78)</td>
<td>43 (1.81)</td>
<td></td>
<td>0.43</td>
</tr>
<tr>
<td>No</td>
<td>68.1</td>
<td>24 (0.52)</td>
<td>53 (1.16)</td>
<td></td>
<td>0.44</td>
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<tr>
<td>Framingham 10-yr CHD risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&lt;0.8</td>
<td>32.7</td>
<td>8 (0.35)</td>
<td>17 (0.77)</td>
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<td>0.46</td>
</tr>
<tr>
<td>0.8–3.6</td>
<td>32.3</td>
<td>11 (0.48)</td>
<td>27 (1.23)</td>
<td></td>
<td>0.39</td>
</tr>
<tr>
<td>&gt;3.6</td>
<td>33.5</td>
<td>23 (1.00)</td>
<td>50 (2.05)</td>
<td></td>
<td>0.50</td>
</tr>
</tbody>
</table>
A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa

The TEMPRANO ANRS 12136 Study Group*

A Primary Outcome

All Patients

<table>
<thead>
<tr>
<th>Treatment</th>
<th>30-Mo Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deferred ART</td>
<td>14.1%</td>
</tr>
<tr>
<td>Deferred ART + IPT</td>
<td>8.8%</td>
</tr>
<tr>
<td>Early ART</td>
<td>7.4%</td>
</tr>
<tr>
<td>Early ART + IPT</td>
<td>5.7%</td>
</tr>
</tbody>
</table>

Patients with Baseline CD4+ Count ≥500/mm³

<table>
<thead>
<tr>
<th>Treatment</th>
<th>30-Mo Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deferred ART</td>
<td>12.4%</td>
</tr>
<tr>
<td>Deferred ART + IPT</td>
<td>7.4%</td>
</tr>
<tr>
<td>Early ART</td>
<td>6.9%</td>
</tr>
<tr>
<td>Early ART + IPT</td>
<td>4.6%</td>
</tr>
</tbody>
</table>

DOI: 10.1056/NEJMoa1507198
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# A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa

The TEMPRANO ANRS 12136 Study Group*

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Early ART (groups 3 and 4)</th>
<th>Deferred ART (groups 1 and 2)</th>
<th>Adjusted Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All patients</strong></td>
<td>no. of patients</td>
<td>person-yr</td>
<td>rate</td>
</tr>
<tr>
<td>Death or severe HIV-related illness (primary outcome)</td>
<td>64</td>
<td>2313</td>
<td>2.8</td>
</tr>
<tr>
<td>Death</td>
<td>21</td>
<td>2520</td>
<td>0.8</td>
</tr>
<tr>
<td>Death or AIDS</td>
<td>50</td>
<td>2333</td>
<td>2.1</td>
</tr>
<tr>
<td>AIDS</td>
<td>33</td>
<td>2333</td>
<td>1.4</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>28</td>
<td>2337</td>
<td>1.2</td>
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<tr>
<td>Invasive bacterial diseases</td>
<td>14</td>
<td>2358</td>
<td>0.6</td>
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<tr>
<td>Other grade 3 or 4 adverse event (main secondary outcome)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 6 mo after randomization</td>
<td>43</td>
<td>489</td>
<td>8.8</td>
</tr>
<tr>
<td>6–30 mo after randomization</td>
<td>27</td>
<td>1775</td>
<td>1.5</td>
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<tr>
<td>Patients with baseline CD4+ count &lt; 500/mm³</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Death or severe HIV-related illness (primary outcome)</td>
<td>23</td>
<td>966</td>
<td>2.4</td>
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<tr>
<td>Death or AIDS</td>
<td>19</td>
<td>972</td>
<td>1.9</td>
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<tr>
<td>AIDS</td>
<td>14</td>
<td>972</td>
<td>1.4</td>
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<tr>
<td>Tuberculosis</td>
<td>12</td>
<td>974</td>
<td>1.2</td>
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<tr>
<td>Invasive bacterial diseases</td>
<td>5</td>
<td>983</td>
<td>0.5</td>
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<tr>
<td>Other grade 3 or 4 adverse event (main secondary outcome)</td>
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<td></td>
</tr>
<tr>
<td>&lt; 6 mo after randomization</td>
<td>12</td>
<td>206</td>
<td>5.8</td>
</tr>
<tr>
<td>6–30 mo after randomization</td>
<td>15</td>
<td>742</td>
<td>2.0</td>
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<tr>
<td>Patients with baseline CD4+ count &lt; 500/mm³</td>
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<tr>
<td>Death or severe HIV-related illness (primary outcome)</td>
<td>41</td>
<td>1347</td>
<td>3.0</td>
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<tr>
<td>Death or AIDS</td>
<td>31</td>
<td>1361</td>
<td>2.3</td>
</tr>
<tr>
<td>AIDS</td>
<td>19</td>
<td>1361</td>
<td>1.4</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>16</td>
<td>1303</td>
<td>1.2</td>
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<tr>
<td>Invasive bacterial diseases</td>
<td>9</td>
<td>1373</td>
<td>0.7</td>
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<tr>
<td>Other grade 3 or 4 adverse event (main secondary outcome)</td>
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<tr>
<td>&lt; 6 mo after randomization</td>
<td>31</td>
<td>283</td>
<td>10.9</td>
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<tr>
<td>6–30 mo after randomization</td>
<td>12</td>
<td>1034</td>
<td>1.2</td>
</tr>
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</table>
What to Start: Initial Combination Regimens for the Antiretroviral-Naive Patient

(Last updated January 28, 2016; last reviewed January 28, 2016)

Panel’s Recommendations

- An antiretroviral regimen for a treatment-naive patient generally consists of two nucleoside reverse transcriptase inhibitors in combination with a third active antiretroviral drug from one of three drug classes: an integrase strand transfer inhibitor, a non-nucleoside reverse transcriptase inhibitor, or a protease inhibitor with a pharmacokinetic enhancer (cobicistat or ritonavir).

- The Panel classifies the following regimens as Recommended regimens for antiretroviral-naive patients:
  
  **Integrase Strand Transfer Inhibitor-Based Regimens:**
  - Dolutegravir/abacavir/lamivudine<sup>3</sup>—only for patients who are HLA-B*5701 negative (AI)
  - Dolutegravir plus tenofovir disoproxil fumarate/emtricitabine<sup>3</sup> (AI)
  - Elvitegravir/cobicistat/tenofovir alafenamide/emtricitabine—only for patients with pre-antiretroviral therapy CrCl ≥30 mL/min (AI)
  - Elvitegravir/cobicistat/tenofovir disoproxil fumarate/emtricitabine—only for patients with pre-antiretroviral therapy CrCl >70 mL/min (AI)
  - Raltegravir plus tenofovir/emtricitabine<sup>3</sup> (AI)

  **Protease Inhibitor-Based Regimen:**
  - Darunavir/ritonavir plus tenofovir disoproxil fumarate/emtricitabine<sup>3</sup> (AI)
DHHS evidence ratings & ART categories

- **Recommendations**
  - A. Strong
  - B. Moderate
  - C. Optional

- **Evidence**
  - I. RCT
  - II. Observational studies
  - III. Expert opinion

- **First-line ART regimen categories**
  - **Recommended**: RCTs show efficacy/durability; favorable tolerability/toxicity
  - **Alternative**: Effective & tolerable, but with potential disadvantages; may be preferred for some patients.
What to start?
**Recommended first-line regimens**

<table>
<thead>
<tr>
<th>INSTI-based</th>
<th>DTG/ABC/3TC(^1)</th>
<th>DTG + TDF/FTC</th>
<th>EVGc/TDF/FTC(^2)</th>
<th>EVGc/TAF/FTC(^3)</th>
<th>RAL + TDF/FTC</th>
<th>AI</th>
</tr>
</thead>
</table>

| PI-based                         | DRVr + TDF/FTC    | AI             |                   |                   |               |      |

\(^1\)If HLA-B57*01 NEGATIVE
\(^2\)If CrCl ≥70 mL/min
\(^3\)If CrCl ≥30 mL/min
# Recommended first-line ART regimen components - INSTIs

<table>
<thead>
<tr>
<th></th>
<th>PROS</th>
<th>CONS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INSTI</strong></td>
<td>• Good virologic response</td>
<td>• BID dosing (RAL)</td>
</tr>
<tr>
<td>- DTG</td>
<td>• Well tolerated/few AEs</td>
<td>• Low resistance barrier (RAL &amp; EVG)</td>
</tr>
<tr>
<td>- EVGc</td>
<td>• Few drug-drug interactions</td>
<td>• Less experience w/ class</td>
</tr>
<tr>
<td>- RAL</td>
<td>• Preserves PIs/NNRTIs</td>
<td>• Requires boosting (EVG)</td>
</tr>
<tr>
<td></td>
<td>• High resistance barrier (DTG)</td>
<td>• Potential CYP3A drug-interactions with COBI</td>
</tr>
<tr>
<td></td>
<td>• DTG “superior” to EFV &amp; DRVr</td>
<td>• AEs: myopathy/rhabdo, skin reactions</td>
</tr>
</tbody>
</table>
Recommended first-line ART regimen components - PIs

<table>
<thead>
<tr>
<th>PROS</th>
<th>CONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>• QD dosing</td>
<td>• ↑ metabolic effects</td>
</tr>
<tr>
<td>• High resistance barrier</td>
<td>• GI intolerance</td>
</tr>
<tr>
<td>• Resistance uncommon w/ failure</td>
<td>• Drug-drug interactions (CYP3A)</td>
</tr>
<tr>
<td>• Experience w/ class</td>
<td>• ↑ pill burden</td>
</tr>
<tr>
<td>• Preserves IIs/NNRTIs</td>
<td></td>
</tr>
</tbody>
</table>

PI - DRVr
### What to start?

**Alternative first-line regimens**

<table>
<thead>
<tr>
<th>NNRTI-based</th>
<th>EFV/TDF/FTC</th>
<th>RPV/TDF/FTC&lt;sup&gt;1&lt;/sup&gt;</th>
<th>BI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PI-based</th>
<th>ATV&lt;sub&gt;r&lt;/sub&gt; + TDF/FTC</th>
<th>ATV&lt;sub&gt;c&lt;/sub&gt; + TDF/FTC&lt;sup&gt;2&lt;/sup&gt;</th>
<th>DRV&lt;sub&gt;r&lt;/sub&gt; + ABC/3TC&lt;sup&gt;3&lt;/sup&gt;</th>
<th>DRV&lt;sub&gt;c&lt;/sub&gt; + TDF/FTC&lt;sup&gt;2&lt;/sup&gt;</th>
<th>DRV&lt;sub&gt;c&lt;/sub&gt; + ABC/3TC&lt;sup&gt;2,3&lt;/sup&gt;</th>
<th>BI</th>
<th>BII</th>
<th>BIII</th>
</tr>
</thead>
</table>

<sup>1</sup>If HIV RNA <100,000 cps/mL & CD4 cells >200/mm³

<sup>2</sup>If CrCl ≥70 mL/min

<sup>3</sup>If HLA-B57*01 NEGATIVE
TAF – The newest NRTI

- **Tenofovir AlaFenamide**
  - Pro-drug of active TFV
  - More stable in plasma
  - Intracellular metabolism
  - Increased bioavailability with cobicistat

[Graph showing concentration over time for TDF and TAF with error bars]

August 1, 2015.
Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, phase 3, non-inferiority trials

Virologic efficacy

---

A

Virological outcome

- E/C/F/TAF (n=866)
- E/C/F/TDF (n=867)

<table>
<thead>
<tr>
<th>Success</th>
<th>Failure</th>
<th>No data</th>
</tr>
</thead>
<tbody>
<tr>
<td>92</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>90</td>
<td>6</td>
<td>6</td>
</tr>
</tbody>
</table>

E/C/F/TAF was non-inferior to E/C/F/TDF at week 48 in each study
- Study 104: 93% E/C/F/TAF vs 92% E/C/F/TDF, difference (95% CI) 1.0% (-2.6 to 4.5)
- Study 111: 92% E/C/F/TAF vs 89% E/C/F/TDF, difference (95% CI) 3.1% (-1.0 to 7.1)

Lancet 2015; 385: 2606-15
Published Online April 16, 2015
http://dx.doi.org/10.1016/S0140-6736(15)60616-X
Renal & bone effects

**Urine (protein): creatinine ratio**
- Protein (UPCR)
- Albumin (UA CR)
- Retinol binding protein
- β2-microglobulin

**Mean (SD) % change from baseline**

- **Baseline**
  - 44 mg/g
  - 5 mg/g

- **E/C/F/TAF**
  - 64 µg/g
  - 67 µg/g

- **E/C/F/TDF**
  - 101 µg/g
  - 103 µg/g

**Spine**
- p<0.0001
- p=0.0001

Source: Lancet 2015; 385: 2606-15

Published Online
April 16, 2015
http://dx.doi.org/10.1016/S0140-6736(15)60616-X
TAF forms available

TAF/FTC/EVGc

TAF/FTC/RPV

TAF/FTC
What to start?

- Questions to consider:
  - Baseline renal insufficiency?
    - Avoid TDF – use ABC or TAF
    - Avoid cobicistat with TDF if CrCl ≤70 mL/min
    - Avoid cobicistat if CrCl ≤30 mL/min
  - Importance of pill burden?
    - Single pill?
    - QD vs. BID?
  - GERD/acid suppression?
    - Avoid ATV and RPV
  - Sulfa allergy?
    - Caution with DRV?
      - DRV allergy rare (<2%); more frequent with TMP-SMX allergy (OR>4)
  - Drug interactions?

## Monitoring after ART initiation

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Timepoint/Frequency of Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Entry into Care</td>
</tr>
<tr>
<td>HIV Serology</td>
<td>✓</td>
</tr>
<tr>
<td>CD4 Count</td>
<td>✓</td>
</tr>
<tr>
<td>HIV Viral Load</td>
<td>✓</td>
</tr>
<tr>
<td>Resistance Testing</td>
<td>✓</td>
</tr>
<tr>
<td>HLA-B*5701 Testing</td>
<td>✓</td>
</tr>
</tbody>
</table>

- If HIV diagnosis has not been confirmed
- During first 2 years of ART or if viremia develops while patient on ART or CD4 count < 300 cells/mm³
- After 2 years on ART with consistently suppressed viral load:
  - CD4 Count 300–500 cells/mm³:
    - Every 12 months
  - CD4 Count > 500 cells/mm³:
    - CD4 monitoring is optional

Drug-drug interactions:
All PIs are CYP3A4 inhibitors

Contraindicated
• Statins
  Simvastatin
  Lovastatin
• Fluticasone
• Rifampin
• Amiodarone
• Triazolam
• Quindine

Major Interactions
• Phosphodiesterase Type 5 inhibitors
• Oral Contraceptives
• Azole Antifungals
• NNRTIs
• Methadone
• Anticonvulsants
• Rifabutin
• Midazolam
Summary

• ART characteristics
  – Potency
  – Adverse events
  – Tolerability
  – Resistance

• Start ART as early as possible

• Use “recommended” regimens unless there is a compelling reason not to
  – See Table 7 in the DHHS Guidelines
Basics of HIV Resistance

Southeast AIDS Education & Training Center
HIV Clinical Overview
12 May 2016

Todd Hulgan, MD, MPH
Department of Medicine, Division of Infectious Diseases
Vanderbilt University School of Medicine
Tennessee Center for AIDS Research (TN-CFAR)
Tennessee Valley Veterans Healthcare System

todd.hulgan@vanderbilt.edu
Objectives

• Define the basics of HIV resistance
  – How...does resistance develop?
  – When...is resistance testing recommended?
  – [Viral fitness and reversion]
  – What...should I use to test for resistance?
  – Who...are patients with resistance?
  – Where...do I go for more information?
How do we characterize ART?

• Resistance:
  – Development of genetic mutations in viral DNA that make that strain less sensitive to a drug
  – Drugs have different *thresholds* to resistance.
    • High threshold = several steps need to take place for a viral strain to become resistant
    • Medications with a “low threshold” should be combined with potent active agents in a regimen
How does resistance develop?

- Insufficient drug level
- Viral replication in the presence of drug
- Resistant virus

Factors:
- Poor adherence
- Social/personal issues
- Regimen issues
- Toxicities

Causes:
- Host genetics
- Poor potency
- Wrong dose
- Poor absorption
- Rapid clearance
- Poor activation
- Drug interactions
How does resistance develop?

Continuation of a failing ART regimen after early resistance has developed selects for expansion of resistance.
True or False?

The patients with the lowest levels of adherence are the most likely to develop resistance to their ARVs
What is the relationship between adherence and resistance?
Testing for Drug Resistance

- Before initiation of ART:
  - **Transmitted resistance in 6-16% of HIV-infected patients**
  - In absence of therapy, resistance mutations may decline over time and become undetectable by current assays, but may persist and cause treatment failure when ART is started
  - Identification of resistance mutations may optimize treatment outcomes
  - **Resistance testing (genotype) recommended for all at entry to care**
  - Recommended for all pregnant women

- Patients with virologic failure:
  - Perform **while patient is taking ART, or ≤4 weeks after discontinuing therapy**
  - Interpret in combination with history of ARV exposure and ARV adherence
Treatment-Experienced Patients: Virologic Failure, Definitions

- **Virologic failure:**
  - Inability to achieve or maintain HIV RNA <200 copies/mL
- **Incomplete virologic response:**
  - Confirmed HIV RNA ≥200 copies/mL after 24 weeks on ART
- **Virologic rebound:**
  - Confirmed HIV RNA ≥200 copies/mL after virologic suppression
- **Virologic blip:**
  - An isolated detectable HIV RNA level that is followed by a return to virologic suppression
- **Virologic suppression:**
  - Confirmed HIV RNA below LLOD (eg, <50 copies/mL)
Treatment-Experienced Patients: Management of Virologic Failure

- Carefully assess causes of virologic failure; management will vary according to cause
- Check HIV RNA, CD4 count, ART history, prior and current ARV resistance test results
  - Resistance test should be done while patient is taking the failing regimen, or within 4 weeks of treatment discontinuation
  - If >4 weeks since ARV discontinuation, resistance testing may still provide useful information, though it may not detect previously selected mutations
HIV fitness

• Fitness can be measured:
  – In the lab:
    – Replicative capacity
  – In the patient
    – Current viral load

• It can explain some phenomena:
  – Meds that shouldn’t be active having an impact:
    • 3TC/FTC, other NRTIs
  – Duration of resistance mutations
Reversion to Predominant Wild-Type Virus After Discontinuing ART

Illustration by David Spach, MD
Drug Resistance Testing: Recommendations

<table>
<thead>
<tr>
<th>RECOMMENDED</th>
<th>COMMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute HIV infection, regardless of whether treatment is to be started</td>
<td>To determine if resistant virus was transmitted; guide treatment decisions. If treatment is deferred, consider repeat testing at time of ART initiation. Genotype preferred.</td>
</tr>
<tr>
<td>Chronic HIV infection, at entry into care</td>
<td>Transmitted drug-resistant virus is common in some areas; is more likely to be detected earlier in the course of HIV infection. If treatment is deferred, consider repeat testing at time of ART initiation. Genotype preferred to phenotype. Consider integrase genotypic resistance assay if integrase inhibitor resistance is a concern.</td>
</tr>
</tbody>
</table>
## Drug Resistance Testing: Recommendations (2)

<table>
<thead>
<tr>
<th>RECOMMENDED</th>
<th>COMMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virologic failure during ART</td>
<td>To assist in selecting active drugs for a new regimen.</td>
</tr>
<tr>
<td></td>
<td>Genotype preferred if patient on 1st or 2nd regimen; add phenotype if known or suspected complex drug resistance pattern.</td>
</tr>
<tr>
<td></td>
<td>If virologic failure on integrase inhibitor or fusion inhibitor, consider specific genotypic testing for resistance to these to determine whether to continue them.</td>
</tr>
<tr>
<td></td>
<td>(Coreceptor tropism assay if considering use of CCR5 antagonist; consider if virologic failure on CCR5 antagonist.)</td>
</tr>
<tr>
<td>Suboptimal suppression of viral load after starting ART</td>
<td>To assist in selecting active drugs for a new regimen.</td>
</tr>
</tbody>
</table>
Drug Resistance Testing: Recommendations (4)

<table>
<thead>
<tr>
<th>NOT USUALLY RECOMMENDED</th>
<th>COMMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>After discontinuation (&gt;4 weeks) of ARVs</td>
<td>Resistance mutations may become minor species in the absence of selective drug pressure.</td>
</tr>
<tr>
<td>Plasma HIV RNA &lt;500 copies/mL</td>
<td>Resistance assays cannot be performed consistently if HIV RNA is low.</td>
</tr>
</tbody>
</table>
Clinical utility of HIV-1 genotyping and expert advice: the Havana trial

What should I use to test for resistance?

1. Genotype

2. Phenotype

3. Virtual phenotype

4. Co-receptor tropism (Trofile®)
Genotype Assay

PATIENT → PLASMA (>200 µL) → total RNA → cDNA → PR/RT GENES (amplicon)

Viral PR/RT gene isolation

RT PCR

Automated DNA sequencing

Sequence interpretation

Codon AAA GAC AGT
Lys Asp Ser

Mutation AAA AAC AGC
Lys Asn Ser

Silent mutation
A mutation at codon #184 in the gene Reverse Transcriptase codes for a Valine residue where normally a Methionine residue is found.

M = Methionine
184 = the codon #
V = Valine
## ViroSeq™ HIV-1 Antiretroviral Drug Resistance Report

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Drug</th>
<th>Evidence of Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NRTI</strong></td>
<td>EPIVIR® (lamivudine, 3TC)</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>EMTRIVA® (emtricitabine, FTC)</td>
<td>None</td>
</tr>
<tr>
<td>RETROVIR® (didanosine, AZT)</td>
<td>Possible Resistance***</td>
<td></td>
</tr>
<tr>
<td>VIDEK® (didanosine, ddI)</td>
<td>Possible Resistance***</td>
<td></td>
</tr>
<tr>
<td>ZERIT® (stavudine, d4T)</td>
<td>Possible Resistance***</td>
<td></td>
</tr>
<tr>
<td>ZIPPED® (abacavir, ABC)</td>
<td>Possible Resistance***</td>
<td></td>
</tr>
<tr>
<td>VIPRAZID® (tenofovir, TDF)</td>
<td>Possible Resistance***</td>
<td></td>
</tr>
<tr>
<td><strong>NNRTI</strong></td>
<td>RESCRIPTOR® (delavirdine DLV)</td>
<td>Resistance</td>
</tr>
<tr>
<td></td>
<td>SUSTIVA® (efavirenz, EFV)</td>
<td>Resistance</td>
</tr>
<tr>
<td></td>
<td>VIRAMUNE® (nevirapine, NVP)</td>
<td>Resistance</td>
</tr>
<tr>
<td></td>
<td>INTELENCE™ (etravirine, ETRI)</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>AGENESAS® (amprenavir, APV)</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>LEXIVA® (foscarnet, FOS)</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>CRULIVAN® (indinavir, IDV)</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>FORTOVASE®/INIVRAS® (saquinavir, SQV)</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>KALETRA® (lopinavir + ritonavir, LPV)</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>PREZISTA® (darunavir, DRV)</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>VIRACEPT® (atazanavir, NFV)</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>REYATAZ® (atazanavir, ATV)</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>APTIVU® (tipranavir, TPV)</td>
<td>None</td>
</tr>
</tbody>
</table>

### Drug Class: Drug Resistance Mutations Identified

- **NRTI**: NM1, T215E
- **NNRTI**: K103N

* NOTE: At least one mutation used to determine Evidence of Resistance for this drug has not been fully validated.
** NOTE: At least one mutation used to determine Evidence of Resistance for this drug has not been clinically verified.
*** NOTE: For at least one mutation used to evaluate Evidence of Resistance for this drug, both notes above apply.

Notes: "Notes on Evidence of Resistance"
Phenotypic Resistance Testing

- Tests viability of a synthetic version of the patient’s HIV in the presence of antiretroviral agents
- Similar to traditional bacterial antibiotic susceptibility assays
- Results reported as fold-change in susceptibility to antiretroviral agents
Phenotype Resistance Testing

Graph showing the inhibition of viral replication (%), with drug concentration on the x-axis and inhibition of viral replication on the y-axis. The graph compares wild-type strain (green) and mutant strain (red) with IC_{50} values for each. The fold resistance is indicated at the 50% inhibition point. Reviewed in Wilson. AIDS Read 2000;10:469.
## Phenotype

<table>
<thead>
<tr>
<th>DRUG</th>
<th>PHENOSENSE™ SUSCEPTIBILITY</th>
<th>Evidence of Susceptibility</th>
<th>Net Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fold Change</td>
<td>Increasing</td>
<td>Drug Susceptibility</td>
</tr>
<tr>
<td>Generic Name</td>
<td>Brand Name</td>
<td>Cutoffs (Lower - Upper)</td>
<td></td>
</tr>
<tr>
<td>Abacavir</td>
<td>Zidovudine</td>
<td>(4.5 - 6.5)</td>
<td>1.27</td>
</tr>
<tr>
<td>Didanosine</td>
<td>Videx</td>
<td>(1.3 - 2.2)</td>
<td>0.88</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>Emtriva</td>
<td>(3.5)</td>
<td>&gt;MAX</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>Epivir</td>
<td>(3.5)</td>
<td>&gt;MAX</td>
</tr>
<tr>
<td>Stavudine</td>
<td>Zerit</td>
<td>(1.7)</td>
<td>0.65</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>Retrovir</td>
<td>(1.9)</td>
<td>0.25</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>Viread</td>
<td>(1.4 - 4)</td>
<td>0.31</td>
</tr>
</tbody>
</table>

**NRTI Mutations**: M184V
## Genotypic vs. Phenotypic Resistance Tests

<table>
<thead>
<tr>
<th></th>
<th>Genotypic</th>
<th>Phenotypic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Basis of test</strong></td>
<td>Detects drug resistance mutations present in relevant viral genes</td>
<td>Measures the ability of a virus to grow in different antiretroviral drug concentrations</td>
</tr>
<tr>
<td><strong>Interpretation</strong></td>
<td>Requires knowledge of mutations selected by individual antiretrovirals and potential for cross-resistance conferred by certain mutations</td>
<td>Visual interpretation by bars indicating susceptibility to individual agents</td>
</tr>
<tr>
<td><strong>Sensitivity</strong></td>
<td>Enhanced sensitivity for detecting mixtures of wild-type and resistant virus</td>
<td>Results reflect susceptibility of dominant viral species</td>
</tr>
<tr>
<td><strong>Availability of results</strong></td>
<td>1-2 wks</td>
<td>2-3 wks</td>
</tr>
<tr>
<td><strong>Relative cost</strong></td>
<td>Lower cost than phenotypic assays</td>
<td>Higher cost than genotypic assays</td>
</tr>
</tbody>
</table>
The Virtual Phenotype

Wild-type HIV

Resistant HIV

Genotype & Phenotype Data

Illustration by David Spach, MD
The Virtual Phenotype

Sample report

Virtual Phenotype™
Genotype with quantitative phenotypic analysis

<table>
<thead>
<tr>
<th>Patient/Sample Details</th>
<th>Test Details</th>
<th>Physician Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Name</td>
<td>Sample Type</td>
<td></td>
</tr>
<tr>
<td>Subject ID</td>
<td>Collection Date</td>
<td></td>
</tr>
<tr>
<td>Sample ID</td>
<td>Receipt Date</td>
<td></td>
</tr>
<tr>
<td>Patient ID</td>
<td>Session</td>
<td></td>
</tr>
<tr>
<td>Birth Date</td>
<td>Report Date</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>Virco ID</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lab ID</td>
<td></td>
</tr>
</tbody>
</table>

Resist ance-associated mutations identified:

Subtype analysis

Clade D

Drug

<table>
<thead>
<tr>
<th>Trade name</th>
<th>Generic name</th>
<th>Matches in database</th>
<th>Proportion of matched samples:</th>
<th>Fold change in IC50 (Cut-off for normal susceptible range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrovir®</td>
<td>Zidovudine</td>
<td>211</td>
<td>25</td>
<td>11.9 (4.0)</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>Lamivudine</td>
<td>452</td>
<td>50</td>
<td>46.7 (4.9)</td>
</tr>
<tr>
<td>Videx®</td>
<td>Didanosine</td>
<td>391</td>
<td>75</td>
<td>1.7 (2.0)</td>
</tr>
<tr>
<td>HAART®</td>
<td>Zalcitabine</td>
<td>393</td>
<td></td>
<td>1.9 (2.0)</td>
</tr>
<tr>
<td>Zidovir®</td>
<td>Stavudine</td>
<td>466</td>
<td></td>
<td>1.4 (1.8)</td>
</tr>
<tr>
<td>Zesetra®</td>
<td>Abacavir</td>
<td>357</td>
<td></td>
<td>3.4 (3.0)</td>
</tr>
<tr>
<td>MRV®</td>
<td>Nevirapine</td>
<td>110</td>
<td></td>
<td>2.8 (8.0)</td>
</tr>
<tr>
<td>Rescriptor®</td>
<td>Delavirdine</td>
<td>110</td>
<td></td>
<td>24.8 (10.0)</td>
</tr>
<tr>
<td>Sustiva®, Stocrin®</td>
<td>Efavirenz</td>
<td>111</td>
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<td>1.3 (6.0)</td>
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Average fold change in susceptibility based on comparison of mutations to a proprietary relational database

Mutations identified

Patient, sample, physician, and laboratory reference fields
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**Tropotype Result**

- **R5**
- **D/M**
- **X4**

Virus uses CCR5 co-receptors to enter the CD4+ cell.

---

**Trofile**—A HIGHLY SENSITIVE TROPISM ASSAY

Trofile is a cell-based approach to determine a patient's HIV co-receptor tropism (or "Tropotype"). Trofile uses the complete gp160 coding region of the HIV-1 envelope protein ensuring that all of the determinants of tropism are tested. CLIA* validation experiments demonstrate that Trofile is 100% sensitive at detecting 0.3% CXCR4-using minor variants.

**Trofile Viral Classification**

Co-receptor tropism is defined as an interaction of a virus with a specific co-receptor on the target cell. To gain entry into CD4+ cells, HIV must bind to the cell surface CD4 receptor and to one of two co-receptors, CCR5 or CXCR4.

- **CCR5 Tropic (R5) HIV-1**
  - Virus uses CCR5 to enter CD4+ cells.
- **CXCR4 Tropic (X4) HIV-1**
  - Virus uses CXCR4 to enter CD4+ cells.
- **Dual/Mixed Tropic (D/M) HIV-1**
  - Dual-tropic viruses can use either CCR5 or CXCR4 to enter CD4+ cells. Mixed-tropic populations contain viruses with two or more tropisms.

**Non-reportable**

Co-receptor tropism could not be determined by the Trofile assay. Common causes of a non-reportable result are viral load <1000 copies/mL, reduced viral fitness, or compromised sample collection/handling.

**CCR5 Co-receptor Antagonists**

This class of drugs binds to CCR5 and blocks CCR5-mediated HIV entry into host cells. Trofile is used to determine whether a CCR5 antagonist may be an appropriate drug for a patient. Several clinical trials of CCR5 antagonists have demonstrated the positive and negative predictive value of Trofile in clinical settings.
## Mutations in the Reverse Transcriptase Gene Associated With Resistance to Reverse Transcriptase Inhibitors (cont’d)

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### Mutations in the Reverse Transcriptase Gene Associated With Resistance to Reverse Transcriptase Inhibitors (cont’d)

#### Nonnucleoside Analogue Reverse Transcriptase Inhibitors (NNRTIs)

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<td>VALKVEY</td>
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</table>

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# Mutations in the Protease Gene Associated With Resistance to Protease Inhibitors

## Atazanavir +/- ritonavir

|        | L  | G  | K  | L  | V  | L  | E  | M  | M  | G  | I  | F  | I  | D  | I  | I  | A  | G  | V  | I  | I  | N  | L  |
|--------|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| 10     | 16 | 20 | 24 | 32 | 33 | 34 | 36 | 46 | 48 | 50 | 53 | 54 | 60 | 62 | 64 | 71 | 73 | 82 | 84 | 85 | 88 | 90 |
| 1      | E  | R  | I  | I  | Q  | I  | V  | L  | L  | E  | V  | L  | V  | C  | A  | V  | V  | S  | M  | L  |   |   |   |
| 2      | M  | F  | I  | F  | L  | L  | V  | M  | I  | S  | V  | T  | T  | F  |   |   |   |   |   |   |   |   |
| 3      | V  | T  | V  | V  | V  | M  | V  | T  | T  | F  |   |   |   |   |   |   |   |   |   |   |   |
| 4      | C  | T  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |

## Darunavir/ritonavir

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# Mutations in the Integrase Gene Associated With Resistance to Integrase Strand Transfer Inhibitors

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<td>Q 155 H H</td>
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</tbody>
</table>

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Updates, user notes, and references available at www.iasusa.org.
**ART resistance pearls**

- **M184V** – Common NRTI mutation; “goes away” quickly
  - Changes viral fitness
- **K103N** – Common NNRTI mutation; “stays around” longer
  - Most common transmitted resistance
- NNRTI resistance can occur after a single dose, and after stopping a co-formulated combination
- Resistance “barrier”: PIs > IIs > NRTIs ≥ NNRTIs
- First-line PI failure *without resistance* can occur – Why?
- Order integrase resistance test separately
- Concept of viral “fitness” and “reversion”
Summary

• **HIV resistance** should be considered at all points of care

• Check resistance using a **genotype**
  – At initial visit (if not already controlled on ART)
  – Before ART start
  – At virologic failure

• **Use external resources and local expertise**
A Brief Review of PrEP & nPEP

Southeast AIDS Education & Training Center
HIV Clinical Overview
12 May 2016

Todd Hulgan, MD, MPH
Department of Medicine, Division of Infectious Diseases
Vanderbilt University School of Medicine
Tennessee Center for AIDS Research (TN-CFAR)
Tennessee Valley Veterans Healthcare System
todd.hulgan@vanderbilt.edu
Objectives

• Recognize US guidelines for pre-exposure prophylaxis (PrEP) and non-occupational post-exposure prophylaxis (nPEP)
PrEP: Pre-Exposure Prophylaxis

• How does it work?
  – Uninfected person takes ART
  – May prevent replication of virus & infection

• Daily dosing of (and adherence to) TDF/FTC
PrEP Studies

• **iPrEX**- mostly MSM, TDF/FTC once-daily reduced the risk of HIV infection by 42% overall
  – 92% among participants with blood drug levels indicating regular use

• **Partners PrEP and TDF2**- heterosexual couples in Africa, TDF/FTC or TDF alone reduced the risk of HIV acquisition by about 65%-75%

• **Bangkok Tenofovir Study**- IDU, daily TDF alone reduced HIV acquisition among IVDU ~50%

Choopanya *Lancet.* 2013;381(9883):2083
### Table 1: Summary of Guidance for PrEP Use

<table>
<thead>
<tr>
<th>Detecting substantial risk of acquiring HIV infection</th>
<th>Men Who Have Sex with Men</th>
<th>Heterosexual Women and Men</th>
<th>Injection Drug Users</th>
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<tbody>
<tr>
<td>HIV-positive sexual partner</td>
<td>HIV-positive sexual partner</td>
<td>HIV-positive injecting partner</td>
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</tr>
<tr>
<td>Recent bacterial STI</td>
<td>Recent bacterial STI</td>
<td>Sharing injection equipment</td>
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</tr>
<tr>
<td>High number of sex partners</td>
<td>High number of sex partners</td>
<td>Recent drug treatment (but currently injecting)</td>
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</tr>
<tr>
<td>History of inconsistent or no condom use</td>
<td>History of inconsistent or no condom use</td>
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</tr>
<tr>
<td>In high-prevalence area or network</td>
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</tbody>
</table>

| Clinically eligible                                   | Documented negative HIV test result before prescribing PrEP | No signs/symptoms of acute HIV infection | Normal renal function; no contraindicated medications | Documented hepatitis B virus infection and vaccination status |                      |

| Prescription                                           | Daily, continuing, oral doses of TDF/FTC (Truvada), ≤90-day supply |                      |                      |                      |                      |

| Other services                                         | Follow-up visits at least every 3 months to provide the following: | HIV test, medication adherence counseling, behavioral risk reduction support, side effect assessment, STI symptom assessment | At 3 months and every 6 months thereafter, assess renal function | Every 6 months, test for bacterial STIs |                      |

| Do oral/rectal STI testing                             | Assess pregnancy intent | Pregnancy test every 3 months | Access to clean needles/syringes and drug treatment services |                      |                      |

STI: sexually transmitted infection

PrEP: Candidates

Substantial risk of acquiring HIV infection

• Men who have sex with men (MSM)
  – HIV-positive sexual partner
  – Recent bacterial STI
  – High number of sex partners
  – History of inconsistent/no condom use
  – Commercial sex work

PrEP: Candidates

Substantial risk of acquiring HIV infection

• Transgender individuals
  – Engaging in high-risk sexual behaviors

PrEP: Candidates

Substantial risk of acquiring HIV infection

• Heterosexual women and men
  – HIV-positive sexual partner
  – Recent bacterial STI
  – High number of sex partners
  – History of inconsistent/no condom use
  – Commercial sex work
  – High-prevalence area or network

PrEP: Candidates

Substantial risk of acquiring HIV infection

• Injection drug users (IDU)
  – HIV-positive injecting partner
  – Sharing injection equipment
  – Recent drug treatment (but currently injecting)

PrEP: Clinical Eligibility

• Documented negative HIV test
• No signs/symptoms of acute HIV infection
• Normal renal function
• No contraindicated medications
• Documented hepatitis B infection & vaccination status

PrEP: HIV Testing

• Are signs/symptoms of acute HIV present now or in prior 4 weeks?
  – Option 1: retest antibody in one month
  – Option 2: HIV antibody/antigen assay
  – Option 3: HIV-1 viral load

Acute HIV Infection

Symptoms

- Fever
- Fatigue
- Myalgia
- Skin rash
- Headache
- Pharyngitis
- Cervical Lymphadenopathy
- Arthralgia
- Night sweats
- Diarrhea

Providing PrEP

Before starting PrEP:

• Clinical eligibility
• Educate
  – Side effects
  – Limitations
  – Daily adherence
  – Symptoms of seroconversion
  – Monitoring schedule
  – Safety
  – Criteria for discontinuation
• Partner information
• Social history: housing, substance use, mental health, domestic violence

Every visit:
Assess adherence
Risk reduction counseling
Provide condoms

www.hivguidelines.org
Providing PrEP

After confirmation of clinical eligibility:

• Prescribe no more than 90-day supply of PrEP
  – Truvada 1 tablet PO daily
    (TDF 300mg + FTC 200mg)
  – Insurance prior approval?
  – Truvada for PrEP Medication Assistance Program

Discontinuing PrEP

• Positive HIV result
• Acute HIV signs or symptoms
• Non-adherence
• Renal disease
• Changed life situation: lower HIV risk

Updated Guidelines for Antiretroviral Postexposure Prophylaxis After Sexual, Injection Drug Use, or Other Nonoccupational Exposure to HIV—United States, 2016

from the
Centers for Disease Control and Prevention,
U.S. Department of Health and Human Services

http://www.cdc.gov/hiv/guidelines/preventing.html
nPEP

Non-occupational Post-exposure Prophylaxis

• High risk exposure
• ≤72 hours after exposure
• Laboratory evaluation
• 28 day course
• Preferred: TDF/FTC + RAL or DTG
• Follow-up testing

http://www.cdc.gov/hiv/guidelines/preventing.html
• Resources for **ART interactions**:
  – [http://hivinsite.ucsf.edu/interactions](http://hivinsite.ucsf.edu/interactions)

• Resources for **ART resistance interpretation**:
  – [https://www.iasusa.org/content/drug-resistance-mutations-in-HIV](https://www.iasusa.org/content/drug-resistance-mutations-in-HIV)
  – [http://www.aidsetc.org/ppt/p02-et/et-01-00/nw_arv-resist-testing.ppt](http://www.aidsetc.org/ppt/p02-et/et-01-00/nw_arv-resist-testing.ppt)

• Resources for **PrEP & nPEP**
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