ACTHIV 2016: A State-of-the-Science Conference for Frontline Health Professionals
Objectives & Disclosures

At the end of the session, participants will be able to:

• Implement current recommendations for initial antiretroviral therapy regimens in your practice

• Identify common side effects and drug interactions for antiretroviral drug classes and agents

Disclosures

• Advisory Board
  — Gilead Sciences

• Grant/Research Support
  — Janssen Therapeutics
  — Gilead Sciences
Outline

- ART: Making it Work
- Adherence & Approach to the Patient with HIV

Acknowledgement: R Gandhi. ACTHIV 2015.
Case 1

- PT, 39 yo white male IDU
- Found HIV+ during hospital stay for PJP
- CD4 15, VL 125,000
- Stable after 2 weeks IV TMP-SMX + steroids
- He asks you 3 questions:
  - Can you help w/ housing?
  - Can I get addiction treatment?
  - I have no job and no insurance; how will I get by?
Question 1

I. For PT, the 39 yo HIV+ IDU:
Which best describes the likely outcome of ART within 2 weeks for this patient, as compared to no ART?

1. Mortality and morbidity benefit from starting ART in 1st 2 weeks with reliable supply of ART ensured
2. No benefit in mortality and morbidity with ART within the first 2 weeks
3. No benefit in mortality and morbidity with ART within the first 2 weeks, and a higher risk of severe IRIS
4. Poorer clinical outcome, and poorer adherence
5. Something else
• View results in your browser: https://api.cvent.com/polling/v1/api/polls/sp-k4ztg7
Question 1

I. For PT, the 39 yo HIV+ IDU:

Which best describes the likely outcome of ART within 2 weeks for this patient, as compared to no ART?

1. Mortality and morbidity benefit from starting ART in 1st 2 weeks with reliable supply of ART ensured
2. No benefit in mortality and morbidity with ART within the first 2 weeks
3. No benefit in mortality and morbidity with ART within the first 2 weeks, and a higher risk of severe IRIS
4. Poorer clinical outcome, and poorer adherence
5. Something else
Case 2

- BJ, 26 yo black MSM manager
- Tested for work insurance
- Two HIV ELISAs are positive
  - HIV negative 1 yr ago
- CD4 655, VL 18,000
- He asks you 3 questions:
  - When should I start therapy for HIV?
  - How should I be treated?
  - How can you tell if the medicine is working?
Question 2:

II. For BJ, the 28 yo HIV+ manager:
Which best describes the expected outcome of ART for this patient, compared to not starting ART?

1. Improved quality of life
2. Lower risk of infection-related cancers, such as KS, NHL, cervical CA, and Hodgkin’s lymphoma
3. Lower risk of cardiovascular disease and lower Framingham risk score
4. Lower risk of TB and severe bacterial infections
5. Answers # 1, 2 and 4
View results in your browser: https://api.cvent.com/polling/v1/api/polls/sp-7b981o
Question 2:

II. For BJ, the 28 yo HIV+ manager:
Which best describes the expected outcome of ART for this patient, compared to not starting ART?

1. Improved quality of life
2. Lower risk of infection-related cancers, such as KS, NHL, cervical CA, and Hodgkin’s lymphoma
3. Lower risk of cardiovascular disease and lower Framingham risk score
4. Lower risk of TB and severe bacterial infections
5. Answers # 1, 2 and 4
Approach to the HIV+ Patient: 4 Steps

**Step 1**: History, Examination and Lab Tests

**Step 2**: Opportunistic infection prophylaxis (if indicated)

**Step 3**: Antiretroviral therapy: when and what to start; common side effects of ART

**Step 4**: How to monitor a patient on ART
ART: The Basics

• When to start?
  – Treat everyone ASAP
  – Case by case, time limited deferrals may be useful

• What to start? ...A long list of available ART drugs
  – Shorter list of preferred, commonly used regimens
  – Easily broken down into a few steps
When to Start

ART recommended for all HIV+ individuals.
Strength of recommendation AI for all patients.

Panel’s Recommendations

- 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).
- ART is also recommended for HIV-infected individuals to prevent HIV transmission (AI).
- 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.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion

START and TEMPRANO confirm that treatment should be offered irrespective of CD4 cell count

START: Significantly lower incidence of severe bacterial infections, Infection-related cancers, and TB; improved quality of life

**A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa**

The TEMPRANO ANRS 12136 Study Group

**Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection**

The INSIGHT START Study Group

**Patients with Baseline CD4+ Count ≥500/mm³**

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

**Cumulative Probability of Death or Severe HIV-Related Illness (%)**

Months since Randomization

**Time to First Primary Event**

Deferred initiation

Immediate initiation

0.56 (0.33-0.94)

0.43 (0.30-0.62)
ACTG 5164: Immediate (2 wks) vs. Delayed ART (6 wks) with an Acute OI

- 228 pts with a treatable OI
  - Most common OI: PCP (63%)
  - TB excluded; 75% steroids
  - Small number cryptococcal meningitis, Toxoplasmosis

**RESULTS**

- AIDS progression/death: immediate rx (14%) vs. delayed rx (24%)
  - No difference in safety/toxicity, IRIS, or week 48 responses

\[
\text{HR} = 0.53 \\
95\% \text{CI} (0.30 - 0.92) \\
p = 0.02
\]
What to start?
HIV drugs target virus lifecycle

1) Virus Entry
2) Reverse transcriptase
3) Integration
4) Transcription
5) Translation
6) Cleavage
7) Packaging
8) Maturation
9) Re-infection

Source: R Gandhi. ACTHIV 3.28.15
Therapies now available for HIV

1) Virus Entry
2) Reverse transcriptase
3) Integration
4) Transcription
5) Translation
6) Cleavage
7) Packaging
8) Maturation
9) Reverse infection

Viral entry occurs via interaction with CD4 receptors (CXCR4, CCR5).

Nucleoside reverse transcriptase inhibitors (NRTIs):
- e.g. AZT, tenofovir, abacavir

Non-nucleoside reverse transcriptase inhibitors (NNRTIs):
- e.g. efavirenz

Protease inhibitors (PIs):
- e.g. ritonavir, darunavir

Integrate strand transfer inhibitors (INSTIs):
- e.g. raltegravir

Fusion (entry) inhibitor:
- e.g. enfuvirtide

CCR5 receptor antagonist:
- e.g. maraviroc

Source: R Gandhi. ACTHIV 3.28.15
Antiretroviral Therapy: >25 Options

### Violet-combination agents

**Nucleoside and nucleotide RTIs**
- Zidovudine, AZT (*Retrovir*)
- Abacavir, ABC (*Ziagen*)
- Lamivudine, 3TC (*Epivir*)
- Didanosine, ddI (*Videx*)
- Stavudine, d4T (*Zerit*)
- Tenofovir, TDF (*Viread*)
- Emtricitabine, FTC (*Emtriva*)
- AZT/3TC (*Combivir*)
- AZT/3TC/ABC (*Trizivir*)
- ABC/3TC (*Epzicom*)
- TDF/FTC (*Truvada*)

**NNRTIs:**
- Delavirdine (DLV)
- Nevirapine, NVP (*Viramune*)
- Efavirenz, EFV (*Sustiva*)
- Etravirine (*Intence*)
- Rilpivirine (*Edurant*)

**Fusion inhibitors:**
- Enfuvirtide, ENF or T20 (*Fuzeon*)

**Protease inhibitors:**
- Indinavir, IDV (*Crixivan*)
- Saquinavir, SQV (*Invirase*)
- Nelfinavir, NFV (*Viracept*)
- Amprenavir, APV (*Agenerase*)
- Atazanavir, ATV (*Reyataz*)
- Fosamprenavir, FPV (*Lexiva*)
- Lopinavir/ritonavir (*Kaletra*)
- Tipranavir (*Aptivus*)
- Darunavir (*Prezista*)

**6 STRs (1 pill once daily)**
- EFV/FTC/TDF (*Atripla*)
- RPV/FTC/TDF (*Complera*)
- RPV/FTC/TAF (*Odefsey*)
- EVG/cob/FTC/TDF (*Stribild*)
- EVG/cob/FTC/TAF (*Genvoya*)
- DTG/ABC/3TC (*Triumeq*)

**CCR5 receptor blocker**
- Maraviroc (*Selzentry*)

**Integrase inhibitor**
- Raltegravir (*Isentress*)
- Elvitegravir (*EVG*)
- Dolutegravir (DTG) (*Tivicay*)
## Antiretroviral Therapy: Preferred Options

**violet – combination agents**

### Nucleoside and nucleotide RTIs
- Zidovudine, AZT (*Retrovir*)
- Abacavir, ABC (*Ziagen*)
- Lamivudine, 3TC (*Epivir*)
- Didanosine, ddI (*Videx*)
- Stavudine, d4T (*Zerit*)
- Tenofovir, TDF (*Viread*)
- Emtricitabine, FTC (*Emtriva*)
- AZT/3TC (*Combivir*)
- AZT/3TC/ABC (*Trizivir*)
- ABC/3TC (*Epzicom*)
- TDF/FTC (*Truvada*)

### CCR5 receptor blocker
- Maraviroc (*Selzentry*)

### Integrase inhibitor
- Raltegravir (*Isentress*)
- Elvitegravir (EVG/c/F/T)
- Dolutegravir (DTG) (*Tivicay*)

### NNRTIs:
- Delavirdine (DLV)
- Nevirapine, NVP (Viramune)
- Efavirenz, EFV (*Sustiva*)
- Etravirine (*Intelence*)
- Rilpivirine, RPV (*Edurant*)

### Protease inhibitors:
- Indinavir, IDV (*Crixivan*)
- Saquinavir, SQV (*Invirase*)
- Nelfinavir, NFV (*Viracept*)
- Amprenavir, APV (*Agenerase*)
- Atazanavir, ATV (*Reyataz*)
- Fosamprenavir, FPV (*Lexiva*)
- Lopinavir/ritonavir (*Kaletra*)
- Tipranavir (*Aptivus*)
- Darunavir (*Prezista*)

### Fusion inhibitors:
- Enfuvirtide, ENF or T20 (*Fuzeon*)

### 6 STRs (1 pill once daily)
- EFV/FTC/TDF (*Atripla*)
- RPV/FTC/TDF (*Complera*)
- RPV/FTC/TAF (*Odefsey*)
- EVG/cob/FTC/TDF (*Stribild*)
- EVG/cob/FTC/TAF (*Genvoya*)
- DTG/ABC/3TC (*Triumeq*)
How Choose Initial ART?

Common Initial Treatments for HIV

NNRTI:
- Rilpivirine (RPV)* (if VL <100K, CD4>200)
- Efavirenz (EFV)*

or

Three NRTI combos
- Tenofovir disoproxil fumarate (TDF)/FTC
  or
  • Tenofovir alafenamide (TAF)/FTC
  or
  • Abacavir (ABC)/3TC

Boosted PI:
- Darunavir/r (DRV/r or DRV/c)

or

Integrase inhibitor
- Raltegravir
- Elvitegravir/cobi*
- Dolutegravir (DTG)**

*Coformulated with tenofovir/FTC; **Coformulated with ABC/3TC
DHHS Guidelines May 2014: Ten Recommended Regimens

<table>
<thead>
<tr>
<th>NNRTI</th>
<th>1. Efavirenz/emtricitabine/tenofovir DF</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI</td>
<td>2. Atazanavir + ritonavir + emtricitabine/tenofovir DF</td>
</tr>
<tr>
<td></td>
<td>3. Darunavir + ritonavir (QD) + emtricitabine/tenofovir DF</td>
</tr>
<tr>
<td>INSTI</td>
<td>4. Raltegravir + emtricitabine/tenofovir DF</td>
</tr>
<tr>
<td></td>
<td>5. Elvitegravir/cobicistat/emtricitabine/tenofovir DF (E/C/F/TDF)</td>
</tr>
<tr>
<td></td>
<td>6. Dolutegravir + abacavir/lamivudine</td>
</tr>
<tr>
<td></td>
<td>7. Dolutegravir + emtricitabine/tenofovir DF</td>
</tr>
</tbody>
</table>

Additional options if the VL <5 log:

|                  | 8. Efavirenz + abacavir/lamivudine |
|                  | 9. Atazanavir + ritonavir + abacavir/lamivudine |
|                  | 10. Rilpivirine/tenofovir DF/emtricitabine (if CD4 count >200/mm³) |

IAS-USA 2014 Guidelines Concur on All Ten Recommended Regimens

DHHS. Available at: http://aidsinfo.nih.gov/contentfiles/AdultARV_INSTIRecommendations.pdf. Update May 2014
DHHS Guidelines March 2016: Six Recommended Regimens

<table>
<thead>
<tr>
<th>PI</th>
<th>1. Darunavir/ritonavir (DRV/r) + TDF/FTC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2. Dolutegravir/abacavir/lamivudine (DTG/ABC/3TC) only for patients who are HLA-B*5701 negative</td>
</tr>
<tr>
<td></td>
<td>3. DTG + tenofovir disoproxil fumarate/emtricitabine (TDF/FTC)</td>
</tr>
<tr>
<td>INSTI</td>
<td>4. Elvitegravir/cobicistat/TDF/FTC (EVG/c/TDF/FTC) ...only for patients with pre-ART CrCl &gt;70 mL/min</td>
</tr>
<tr>
<td></td>
<td>5. Elvitegravir/cobicistat/TAF/FTC...for pts w/ CrCl &gt; 30 mL/min</td>
</tr>
<tr>
<td></td>
<td>6. Raltegravir (RAL) + TDF/FTC</td>
</tr>
</tbody>
</table>

- On the basis of individual patient characteristics and needs, an Alternative regimen or; less frequently, an Other regimen; may in some instances be the optimal regimen for a patient.

- Given the large number of excellent options for initial therapy, selection of a regimen for a particular patient should be guided by factors such as virologic efficacy, toxicity, pill burden, dosing frequency, drug-drug interaction potential, resistance testing results, comorbid conditions, and cost.

Why the change? 2014 -> 2016? 10 preferred → 6?

- DRV/r is superior to ATV/r (toxicity)
- RAL is superior to DRV/r and ATV/r (toxicity)
- RAL and DTG are superior to EFV (less tox)
- E/C/F/TDF is non-inferior to EFV, PI/r (less tox)
- E/C/F/TAF is non-inferior to E/C/F/TDF (less tox)

- EFV rarely leads to mania, psychosis, suicidal ideation....and there are other options now
Choosing an Antiretroviral Regimen: Two decisions

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

• **Step 2:** Decide on which drug to use within the NNRTI, PI or INSTI class
How Choose Initial ART?  
Common Initial Treatments for HIV

Three NRTI combos

- Tenofovir disoproxil fumarate (TDF)/FTC
  
or

- Tenofovir alafenamide (TAF)/FTC
  
or

- Abacavir (ABC)/3TC

*Coformulated with tenofovir/FTC; **Coformulated with ABC/3TC

TAF approvals 2015-6
E/C/F/TAF (Genvoya)
RPV/F/TAF (Odefsey)

….future
DRV/C/F/TAF
FTC/TAF
Tenofovir Alafenamide (TAF): Plasma & Cell pK

Plasma TFV

Intracellular TFV-DP

TAF vs TDF in E/C/F/TAF, PI/r + FTC/TAF
- non-inferiority between TDF & TAF regimens
- Less osteopenia w/ TAF
- Less tubular proteinuria w/ TAF

Sax P, et al. 22nd CROI; Seattle, WA; February 23-26, 2015. Abst. 143LB.
<table>
<thead>
<tr>
<th>NRTI</th>
<th>PROS</th>
<th>CONS</th>
</tr>
</thead>
</table>
| TDF/FTC   | • Single tablet regimens (STRs) (w/ EFV, RPV, EVG/cobi)  
|           | • Active vs. HBV                               | • Nephrotoxicity (particularly in those receiving other nephrotoxic agents, PIs) |
|           | • Mild lipid lowering                          | • Increased bone loss                          |
| TAF/FTC or ABC/3TC |                                             |                                                 |
# TDF/FTC or TAF/FTC or ABC/3TC

<table>
<thead>
<tr>
<th>NRTI</th>
<th>PROS</th>
<th>CONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF/FTC</td>
<td>• Single tablet regimens (STRs) 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>TAF/FTC</td>
<td>• In STRs – E/C/F/TAF RPV/FTC/TAF</td>
<td>• Only in STRs</td>
</tr>
<tr>
<td></td>
<td>• Less renal, bone tox</td>
<td>• Less clinical experience</td>
</tr>
<tr>
<td></td>
<td>• GFR &gt; 30 mL/min</td>
<td></td>
</tr>
<tr>
<td>NRTI</td>
<td>PROS</td>
<td>CONS</td>
</tr>
<tr>
<td>------------</td>
<td>-----------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>TDF/FTC</td>
<td>• Single tablet regimens (STRs) 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>TAF/FTC</td>
<td>• In STRs – E/C/F/TAF RPV/FTC/TAF</td>
<td>• Only in STRs</td>
</tr>
<tr>
<td></td>
<td>• Less renal, bone tox</td>
<td>• Less clinical experience</td>
</tr>
<tr>
<td></td>
<td>• GFR &gt; 30 mL/min</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>• Co-formulated with DTG</td>
<td>• Some studies, but not all, show association with myocardial infarction</td>
</tr>
</tbody>
</table>
## Individualizing Therapy: Choosing Between NRTIs

<table>
<thead>
<tr>
<th>Factor</th>
<th>Preferred Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal Disease</td>
<td>TAF/FTC, ABC/3TC</td>
</tr>
<tr>
<td>CV disease</td>
<td>Possibly TDF/FTC</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>Possibly TDF/FTC</td>
</tr>
</tbody>
</table>

---

*ACTHIV: The American Conference for the Treatment of HIV*
## Individualizing Therapy:
### Choosing Between NRTIs

<table>
<thead>
<tr>
<th>Factor</th>
<th>Preferred Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal Disease</td>
<td>TAF/FTC, ABC/3TC</td>
</tr>
<tr>
<td>CV disease</td>
<td>Possibly TDF/FTC</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>Possibly TDF/FTC</td>
</tr>
<tr>
<td>Bone disease</td>
<td>TAF/FTC, Possibly ABC/3TC</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>Cost</td>
<td>3TC patent expired in 2010 ABC patent expired in 2012</td>
</tr>
</tbody>
</table>
Summary #1

• Treat all HIV+ patients ASAP
  – Individual and public health benefits

• Ten high quality ART regimens available
  – 6 are ‘recommended’; NO REASON to use other initial ART

• 1st: Choice of NRTIs via common determinants
  – Renal function; HLA B*5701 status; bone toxicity
  – STRs and co-formulations
Question 3: NRTI for PT, 38 yo IDU

- Labs: HLA B*5701 positive
- Creat 1.8, eGFR 50 mL/min
- CD4 15, VL 125,000
- Prefers a single table regimen

Which NRTI backbone should you start?
1. ABC/3TC, as part of DTG/ABC/3TC
2. TDF/FTC, as part of RPV/FTC/TDF
3. TAF/FTC, as part of E/C/F/TAF
4. Something else
• View results in your browser: https://api.cvent.com/polling/v1/api/polls/suq4gd
Question 3: NRTI for PT, 38 yo IDU

• Labs: HLA B*5701 positive
• Creat 1.8, eGFR 50 mL/min
• CD4 15, VL 125,000
• Prefers a single table regimen

Which NRTI backbone should you start?
1. ABC/3TC, as part of DTG/ABC/3TC
2. TDF/FTC, as part of RPV/FTC/TDF
3. TAF/FTC, as part of E/C/F/TAF
4. Something else
Question 4: NRTI for BJ, 28 yo

- Labs: Creat 0.9, eGFR 95 mL/min
- CD4 655, VL 18,000
- HLA B*5701 negative
- Prefers a single table regimen

Which NRTI backbone should you start?

1. ABC/3TC, as part of DTG/ABC/3TC
2. TDF/FTC, as part of RPV/FTC/TDF, or E/C/F/TDF
3. TAF/FTC, as part of E/C/F/TAF
4. Any of the above
5. Something else
• View results in your browser: https://api.cvent.com/polling/v1/api/polls/spp-6h9ca2
Question 4: NRTI for BJ, 28 yo

- Labs: Creat 0.9, eGFR 95 mL/min
- CD4 655, VL 18,000
- HLA B*5701 negative
- Prefers a single table regimen

Which NRTI backbone should you start?

1. ABC/3TC, as part of DTG/ABC/3TC
2. TDF/FTC, as part of RPV/FTC/TDF, or E/C/F/TDF
3. TAF/FTC, as part of E/C/F/TAF
4. Any of the above
5. Something else
How To Choose 3d Drug?

• Individualize ART
  – Pre – ART characteristics (CD4, VL, resistance)
  – ART characteristics
  – Patient co-morbidities

• Refer to *Table VII* in DHHS Guidelines
How Choose 3d Drug? Common Initial Treatments for HIV

I. NNRTI:
Rilpivirine (RPV)* (if VL <100K, CD4>200)
Efavirenz (EFV)*

or

II. Boosted PI:
Darunavir/r (DRV/r or DRV/c)

or

III. Integrase inhibitor
Raltegravir, (RAL)
Elvitegravir/cobi*
Dolutegravir (DTG)**

Three NRTI combos
• Tenofovir (TDF)/FTC
  Plus
  • TAF/FTC
    or
  • Abacavir/3TC

*Coformulated with tenofovir/FTC; **Coformulated with ABC/3TC
ART Considerations

1. Pre-ART
   - CD4, VL, resistance mutations

2. ART Specific
   - Single Tablet Regimen desired?
   - food issues

3. Co-morbidities
   - Renal, bone, neuro-psyche, methadone, CV, lipid
   - Pregnancy (See Perinatal ART GdIns)
## Individualizing Therapy: Choosing a 3rd drug: NNRTI, PI, INSTI

<table>
<thead>
<tr>
<th>Factor</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Need to start ART before resistance results known (acute HIV, OI) or uncertain adherence</td>
<td>Avoid NNRTI; Favor drug with low TDR rate, high resistance barrier: PI, possibly DTG</td>
</tr>
<tr>
<td>Pre-ART VL &gt;100 K, CD4 &lt;200</td>
<td>Avoid RPV</td>
</tr>
<tr>
<td>Food requirements</td>
<td>EFV: empty stomach; RPV with meal (&gt;400 kcal); EVG/cobi/TDF/FTC: with food; DTG: no food requirements</td>
</tr>
<tr>
<td>One pill, once daily desired</td>
<td>DTG/ABC/3TC; EFV/TDF/FTC; EVG/c/TDF/FTC; RPV/TDF/FTC</td>
</tr>
<tr>
<td>HCV Therapy</td>
<td>RAL, DTG: fewer drug interactions</td>
</tr>
</tbody>
</table>
## 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>
</tbody>
</table>

DTG inhibits the organic cation transporter 2 (OCT2) and may increase plasma levels of OCT2 substrates including metformin and dofetilide. Dose adjustment of metformin may be required; dofetilide use is contraindicated.

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>

DTG inhibits the organic cation transporter 2 (OCT2) and may increase plasma levels of OCT2 substrates including metformin and dofetilide. Dose adjustment of metformin may be required; dofetilide use is contraindicated.
“What about side effects?”

- Rash: NNRTIs, bactrim  * CNS: EFV >> RPV, DTG
- Indirect hyperbilirubinemia due to atazanavir
  - Usually asymptomatic. Similar to Gilbert’s; benign
- Nephrotoxicity: rare complication of tenofovir
- Hepatotoxicity – all, does not help w/ choice
- GI: boosted PIs
- Body-fat abnormalities, especially with older ARVs
- Immune reconstitution inflammatory syndrome
  - Worsening or unmasking of opportunistic conditions soon after initiation of ART due to restoration of antigen-specific immunity
  - e.g. TB, MAI lymphadenitis, zoster, PCP, PML, KS
## Common Drug Interactions

<table>
<thead>
<tr>
<th>Non-HIV medication</th>
<th>ARV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proton-pump inhibitors, H2 blockers</td>
<td>↓ atazanavir, rilpivirine absorption</td>
</tr>
<tr>
<td>Divalent cations</td>
<td>Caution with INSTIs</td>
</tr>
</tbody>
</table>

Useful site: http://www.hiv-druginteractions.org
# Common Drug Interactions

## Non-HIV medication

<table>
<thead>
<tr>
<th>Non-HIV medication</th>
<th>ARV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proton-pump inhibitors, H2 blockers</td>
<td>↓ atazanavir, rilpivirine absorption</td>
</tr>
<tr>
<td>Divalent cations</td>
<td>Caution with INSTIs</td>
</tr>
</tbody>
</table>

## ARV

<table>
<thead>
<tr>
<th>ARV</th>
<th>Non-HIV medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protease inhibitors, cobicistat</td>
<td>↑ levels of CYP3A4 metabolized drugs, e.g. many statins, rifampin, PDE5 inhibitors</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>↓ methadone, buprenorphine</td>
</tr>
</tbody>
</table>

Useful site: http://www.hiv-druginteractions.org
### HCV Rx: ARV Interaction Score Card

<table>
<thead>
<tr>
<th></th>
<th>Simeprevir</th>
<th>Sofosbuvir</th>
<th>Ledipasvir</th>
<th>Daclatasvir</th>
<th>P/r/O + D</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DDI</strong></td>
<td>Substrate of CYP3A4, OATP1B1/3</td>
<td>Substrate of P-gp and BCRP</td>
<td>Inhibitor/Substrate of P-gp and BCRP</td>
<td>Inhibitor of OATP1B1/3, BCRP, Substrate of P-gp and CYP3A4</td>
<td>Inhibit/Sub of UGT1A1, OATP1B1/3, BCRP, CYP3A4, CYP2C8, P-gp</td>
</tr>
<tr>
<td><strong>ATV/r</strong></td>
<td>No data</td>
<td>No data</td>
<td>LDV ↓; ATV ↓</td>
<td>DCV ↑*</td>
<td>ATV ↔; ABT450 ↑</td>
</tr>
<tr>
<td><strong>DRV/r</strong></td>
<td>SIM ↑; DRV ↔</td>
<td>SOF ↑; DRV ↔</td>
<td>LDV ↑; DRV ↔</td>
<td>ALLY-2 ↔</td>
<td>DRV ↓; 3D ↓</td>
</tr>
<tr>
<td><strong>LPV/r</strong></td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>ALLY-2 ↔</td>
<td>LPV ↔; ABT450 ↑</td>
</tr>
<tr>
<td><strong>TPV/r</strong></td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td><strong>EFV</strong></td>
<td>SIM ↓; EFV ↔</td>
<td>SOF ↔; EFV ↔</td>
<td>ION-4 ↔</td>
<td>DCV ↓*</td>
<td>No PK data**</td>
</tr>
<tr>
<td><strong>RPV</strong></td>
<td>SIM ↔; RPV ↔</td>
<td>SOF ↔; RPV ↔</td>
<td>LDV ↔; RPV ↔</td>
<td>ALLY-2 ↔</td>
<td>ABT450 ↑; RPV ↑</td>
</tr>
<tr>
<td><strong>ETV</strong></td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td><strong>RAL</strong></td>
<td>SIM ↔; RAL ↔</td>
<td>SOF ↔; RAL ↔</td>
<td>LDV ↔; RAL ↔</td>
<td>ALLY-2 ↔</td>
<td>3D ↔; ↑ RAL</td>
</tr>
<tr>
<td><strong>ELV/cobi</strong></td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td><strong>DTG</strong></td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>ALLY-2 ↔</td>
<td>No data</td>
</tr>
<tr>
<td><strong>MVC</strong></td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td><strong>TDF</strong></td>
<td>SIM ↔; TFV ↔</td>
<td>SOF ↔; TFV ↔</td>
<td>LDV ↔; ↑TFV</td>
<td>DCV ↔; TFV ↔</td>
<td>3D ↔; TFV ↔</td>
</tr>
</tbody>
</table>

* Decrease DCV dose to 30mg QD, Increase DCV dose to 90mg QD, ** 3D + EFV led to premature study discontinuation due to toxicities*  

---  

Slide courtesy of Jennifer Kiser
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.”
ART Options for PT and JB?

• PT
Elvitegravir/cob/FTC/TAF
Take with food
Drug interactions +++
Some GI toxicity
Overlap w/ OI treatment & prophylaxis

• JB
All ‘recommended’ options:
Integrase-based regimen
DTG/ABC/3TC
- Some insomnia, HA reports
E/C/F/TAF (or E/C/F/TDF)
- Benefit: less long term tox
NNRTI-based regimen
RPV/F/TDF or RPV/F/TAF
- w/ large meal
Summary #2

• Individualize Regimen Selection
  – Disease severity, resistance
  – Drug characteristics: food, side effects, interactions
  – STR, once daily, twice daily
  – Pt co-morbidities: HCV; lipids; renal dx; osteopenia; CA

• Engage patient in choice to ensure adherence
Outline

- ART: Making it Work
- Adherence & Approach to the Patient with HIV
## Positive and Negative Predictors of Adherence

<table>
<thead>
<tr>
<th>Positive Predictors</th>
<th>Negative Predictors</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Physician trust</td>
<td>• Active drug or alcohol use</td>
</tr>
<tr>
<td>• Can identify ART agents</td>
<td>• Untreated mental illness (depression)</td>
</tr>
<tr>
<td>• Understands goals of ART</td>
<td>• Chaotic life, homelessness</td>
</tr>
</tbody>
</table>
Useful Adherence Interventions

Recruit family/friends

Weekly pill boxes

Charts, hand outs of ART pictures, actions, MD & advocate opinions (TPA Guide)

• Know your patient!
  – Lifestyle
  – Habits
  – Where are the meds
  – Sleep, meal preferences
  – Privacy & disclosure
  – Low tech WORKS!
Primary Care Guidelines for the Management of Persons Infected With HIV: 2013 Update by the HIV Medicine Association of the Infectious Diseases Society of America

Judith A. Aberg,1 Joel E. Gallant,2,3 Khalil G. Ghanem,3 Patricia Emmanuel,4 Barry S. Zingman,5 and Michael A. Horberg6

1Division of Infectious Diseases and Immunology, New York University School of Medicine, Bellevue Hospital Center, New York; 2Southwest CARE Center, Santa Fe, New Mexico; 3Johns Hopkins University School of Medicine, Baltimore, Maryland; 4Department of Pediatrics, University of South Florida Health, Tampa; 5Albert Einstein College of Medicine, Montefiore Medical Center, Bronx, New York and 6Mid-Atlantic Permanente Research Institute, Rockville, Maryland

Aberg J et al, CID, Nov. 13, 2013
Lab Tests

• Routine tests
• Screening tests for infection
• HIV-specific tests
Lab Evaluation: Routine Tests

- Chemistries, BUN/Cr, liver function tests
- CBC/diff
- Fasting lipids and glucose
- G6PD: blacks; males from Mediterranean, India, SE Asia
- Urinalysis (U/A)


Aberg J et al, CID, 2013
Lab Evaluation: Screening for Infection

• Serologic testing for infections that can reactivate: toxoplasma IgG, cytomegalovirus (CMV) IgG

• Hepatitis serologies (A, B, C)

• Tuberculin skin test (TST) or interferon-gamma release assay (IGRA)
  - TST >5 mm is positive in HIV+ patients
  - If negative and patient’s CD4 count is <200, repeat TST or IGRA after immune reconstitution

• STI screen: syphilis; gonorrhea, chlamydia


Aberg J et al, CID, 2013
Lab Evaluation: HIV-specific Tests

- CD4 cell count
- HIV RNA (“viral load” or VL)
- HIV drug resistance test (genotype)
  - Transmitted Drug Resistance (TDR): 16%, non-nucleoside reverse transcriptase inhibitors (NNRTI) (8%); nucleoside RTI (7%)\(^1\)
  - IAS USA: www.iasusa.org/content/hiv-drug-resistance-mutations
  - Stanford HIV Drug Resistance: http://hivdb.stanford.edu/
- HLA-B5701: if considering abacavir.
  - Positive in 8% of US whites; 2% of US African-Americans and Hispanics\(^2\)

DHHS guidelines for use of antiretroviral agents in HIV-1-infected adults and adolescents.
http://AIDSinfo.nih.gov;

\(^1\)Kim D et al, CROI 2013, Abs #149; \(^2\)E Phillips, CID, 2006
Monitoring after Starting ART

- Chemistries, BUN/Cr, LFTs: **wk 2-8 after starting ART, 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.**

Urinalysis and Renal Monitoring

• U/A at initiation of care and then at least annually (every 6 months if receiving tenofovir)
  • Estimate glomerular filtration rate with serum Cr or measure creatinine clearance
  • Cobicistat, dolutegravir, trimethoprim can inhibit creatinine secretion → ↑ serum Cr without affecting renal function
• Tenofovir nephrotoxicity
  – **Glomerular**: decreased kidney function
  – **Tubular**: Fanconi’s syndrome: glucosuria (with normal blood glucose), proteinuria (≥1+), urinary phosphate wasting

Tourret J et al, JASN, 2013
Monitoring after Starting ART

• HIV RNA:
  – 2-4 wks after starting ART; then every 4-8 wks until undetectable.
  – First 2 yrs of ART: every 3-4 mo.
  – After 2 yrs of suppression, can extend to every 6 mo.

• CD4 count:
  – 3 mo. after initiating ART
  – First 2 yrs of ART: every 3-6 mo
  – After 2 yrs of virologic suppression, CD4 300-500: every 12 mo.; CD4 >500, optional

Approach to HIV+ Patient: 4 Steps

**Step 1**: History, Examination, Labs

**Step 2**: OI Prophylaxis for PT
- TMP-SMX DS QD for PCP Prophylaxis
- azithromycin 1200 mg weekly for MAC Pro

**Step 3**: ART – individualizing therapy
- All options open to BJ; individualize choice
- Fewer options for PT; no ABC, no TDF
  - Individualize remaining choices

**Step 4**: Monitoring
Summary

• Treat all HIV+ patients with ART

• To select ART:
  – Start w/ NRTI choice
  – Individualize regimen (a few simple choices)

• Common decision points
  – Patient characteristics, stage of HIV, co-morbidities
  – Food issues, drug side effects
  – Single tablet regimen? Drug interactions
  – Ensure patient engagement & adherence

• Address HIV primary care issues
Thank you
ACTHIV 2016: A State-of-the-Science Conference for Frontline Health Professionals