Antiretroviral Therapy Initiation:
From Guidelines to Practice: “ART 101”

Medical Care of Vulnerable and Underserved Populations: CME Course

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Disclosures

• Research grant support from National Institutes for Health (NIH), Centers for Disease Control (CDC) & President’s Emergency Plan for AIDS Relief (PEPFAR) –
  – For work ongoing in East Africa related to HIV care models
  – This disclosure is unrelated to this presentation
Goals

• To create a working proficiency in selecting initial ART regimens for non-HIV specialists, including how and when to access specialists

• Review DHHS first line & alternate regimens for HIV treatment
  – Pros and cons, considerations, choices
  – Many updates from last year (4 new drugs FDA approved in 2018)

• Will not focus on:
  – In-depth ART pharmacology
  – HIV drug resistance
  – Optimizing ART regimens in virally suppressed individuals
  – 2-drug or “Nucleoside-sparing” regimens
  – ART for pediatric or pregnant patients
  – Drugs in development but not yet FDA approved

• 50 minutes... lots to cover!
• Reach out to your ID colleagues anytime for discussion and optimization on ART!
• Take-home points summarized on the yellow slides
General Resources for HIV ART

• HIV Warm Line/National Clinician Consultation Center:
  – [http://nccc.ucsf.edu/](http://nccc.ucsf.edu/), Telephone: (800) 933-3413, M-F, 6 a.m. – 5 p.m. Pacific time

• For SF Health Network Providers:
  – Send eConsult to SFGH Infectious Diseases Clinic

• HIV drug interactions checker
  – University of Liverpool: [https://www.hiv-druginteractions.org/](https://www.hiv-druginteractions.org/)

• HIV drug resistance database/checker
  – Stanford University:
    – [https://hivdb.stanford.edu/hivdb/by-mutations/](https://hivdb.stanford.edu/hivdb/by-mutations/)
Recommended Initial Regimens for Most People with HIV

Recommended regimens are those with demonstrated durable virologic efficacy, favorable tolerability and toxicity profiles, and ease of use.

**INSTI plus 2 NRTIs:**

- **BIC/TAF/FTC (AI)**
- **DTG/ABC/3TC (AI)*—if HLA-B*5701 negative**
- **DTG plus tenofovir²/FTC (AI for both TAF/FTC and TDF/FTC)**
- **RAL³ plus tenofovir²/FTC (BI for TDF/FTC, BII for TAF/FTC)**

*Note: For individuals of childbearing potential, see Table 6b before prescribing one of these regimens.

**Recommended Initial Regimens in Certain Clinical Situations**

These regimens are effective and tolerable, but have some disadvantages when compared with the regimens listed above, or have less supporting data from randomized clinical trials. However, in certain clinical situations, one of these regimens may be preferred.

**INSTI plus 2 NRTIs:**
- **EVG/c/tenofovir²/FTC (BI for both TAF/FTC and TDF/FTC)**
- **RAL plus ABC/3TC (CII)—if HLA-B*5701 negative and HIV RNA <100,000 copies/mL**

*Boosted PI plus 2 NRTIs: (In general, boosted DRV is preferred over boosted ATY)*
- **(DRV/c or DRV/r) plus tenofovir²/FTC (AI)**
- **(ATV/c or ATV/r) plus tenofovir²/FTC (BI)**
- **(DRV/c or DRV/r) plus ABC/3TC**—if HLA-B*5701 negative (BII)

**NNRTI plus 2 NRTIs:**
- **DOR/TDF³/3TC (BI) or DOR plus TAF²/FTC (BII)**
- **EFV plus TDF²/FTC (BI for EFV 600 mg/TDF/FTC or EFV 600 mg/TDF/3TC, BII for EFV 600 mg plus TAF/FTC)**
- **RPV/tenofovir²/FTC (BI)—if HIV RNA <100,000 copies/mL and CD4 cell count >200 cells/mm³**

Regimens to Consider when ABC, TAF, and TDF Cannot be Used or Are Not Optimal:
- **DTG plus 3TC (BI)**
- **DRV/r plus RAL BID (CI)—if HIV RNA <100,000 copies/mL and CD4 cell count >200 cells/mm³**
- **DRV/r once daily plus 3TC² (CI)**

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**Adapted Footnotes:**

a 3TC may be substituted for FTC, or vice versa. ABC/3TC, TDF/3TC, TDF/FTC, TAF/FTC are available as tablets, and as part of single tablet regimens. Cost, access, and availability of STRs can influence choice of 3TC vs FTC.

b TAF and TDF are two forms of tenofovir approved by the FDA. TAF has fewer bone and kidney toxicities than TDF, while TDF is associated with lower lipid levels. Safety, cost, and access are among the factors to consider when choosing between these drugs.

c RAL can be given as 400 mg BID or 1200 mg (two 600-mg tablets) once daily.
U.S. DHHS Guideline Update: October, 2018

<table>
<thead>
<tr>
<th>Initial Regimens “for Most People”</th>
<th>Initial Regimens “in Certain Clinical Situations”</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BIC/TAF/FTC</strong></td>
<td><strong>EVG/cobi + (TDF/FTC or TAF/FTC)</strong></td>
</tr>
<tr>
<td>* If reproductive potential, consult guidance</td>
<td>* If reproductive potential, consult guidance</td>
</tr>
<tr>
<td><strong>DTG/ABC/3TC</strong></td>
<td><strong>RAL/ABC/3TC</strong></td>
</tr>
<tr>
<td>Only if HLB57-01 negative</td>
<td>Only if HLAB57 negative and VL&lt;100,000</td>
</tr>
<tr>
<td>* If reproductive potential, consult guidance</td>
<td>* If reproductive potential, consult guidance</td>
</tr>
<tr>
<td><strong>DTG + (TDF/FTC or TAF/FTC)</strong></td>
<td><strong>(DRV/RTV or DRV/cobi) + (TDF/FTC or TAF/FTC)</strong></td>
</tr>
<tr>
<td>* If reproductive potential, consult guidance</td>
<td></td>
</tr>
<tr>
<td><strong>RAL + (TDF/FTC or TAF/FTC)</strong></td>
<td><strong>(DRV/cobi or DRV/RTV) + ABC/3TC</strong></td>
</tr>
<tr>
<td>Only if HLAB57 negative and VL&lt;100,000</td>
<td>Only if HLB57-01 negative</td>
</tr>
<tr>
<td>* If reproductive potential, consult guidance</td>
<td></td>
</tr>
</tbody>
</table>

Organizational comments:
- BIC/TAF/FTC new in 2018...
- DRV moved out of first line list in 2017...
- EVG/cobi/TAF/FTC and EVG/cobi/TDF/FTC moved out of first line in 2018...
- Guidelines don’t really emphasize TAF vs. TDF much...

Adapted from: US DHHS ART Guidelines – October 28, 2018 Update
### FDA-Approved ARVs, 2018

#### NRTI (nucleoside analogs)
- Tenofovir alafenamide (TAF)
- Tenofovir (TDF)
- Abacavir (ABC)
- Emtricitabine (FTC)
- Lamivudine (3TC)
- Stavudine (D4T)
- Didanosine (DDI)
- Zalcitabine (DDC)
- Zidovudine (ZDV)

#### NNRTI (non-nucleosides)
- Rilpivirine (RPV)
- Etravirine (ETR)
- Doravirine (DOR)
- Efavirenz (EFV)
- Nevirapine (NVP)
- Delavirdine (DLV)

#### Protease Inhibitors
- Darunavir (DRV)
- Atazanavir (ATV)
- Ritonavir (RTV)
- Cobicistat (Cobi)
- Lopinavir (LPV)
- Fosamprenavir (FPV)
- Amprenavir (APV)
- Tipranavir (TPV)
- Nelfinavir (NFV)
- Saquinavir (SQV)
- Indinavir (IDV)

#### Integrase Inhibitors
- Bictegravir (BIC)
- Dolutegravir (DTG)
- Elvitegravir (EVG)
- Raltegravir (RAL)

#### CCR5 Inhibitors
- Maraviroc (MVC)

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

#### Monoclonal Antibody
- Ibalizumab (IBA)
# ARVs in Common Use, 2018

## New FDA Approvals in 2018

- **2/18**: Bictegravir (BIC)
- **3/18**: Ibalizumab: monoclonal Ab (IBA)
- **7/18**: TAF/FTC/cobicistat/DRV (Symtuza)
- **8/18**: Doravirine (DOR)

## NRTI (nucleoside analogs)

- Tenofovir alafenamide (TAF)
- Tenofovir (TDF)
- Abacavir (ABC)
- Emtricitabine (FTC)
- Lamivudine (3TC)

## NNRTI (non-nucleosides)

- Rilpivirine (RPV)

## Protease Inhibitors

- Darunavir (DRV)
- Atazanavir (ATV)
- Ritonavir (RTV)
- Cobicistat (Cobi)

## Integrase Inhibitors

- Bictegravir (BIC)
- Dolutegravir (DTG)
- Elvitegravir (EVG)
- Raltegravir (RAL)
Basic Initial Regimen Composition

Previously:

2x NRTI
- TDF/FTC
  - or
- ABC/3TC

NNRTI
- EFV
- RPV

or

PI
- r/ATV
- r/DRV

or

INSTI
- RAL
- EVG
- DTG

Currently:

2x NRTI
- TAF/FTC
  - or
- TDF/FTC
  - or
- ABC/3TC

INSTI
- BIC
- DTG
- RAL

or

PI
- r/DRV
NRTI’s
NRTI’s: Tenofovir-based Meds

TDF/FTC (Truvada)

- **Renal Concerns**
  - Decrease in eGFR over time?
  - Risk of tubular toxicity/Fanconi’s syndrome?

- **Bone Concerns**
  - Decrease in bone density?
  - Concomitant increase risk of fracture?

TAF/FTC (Descovy)

- **Renal Profile**
  - better?

- **Bone Profile**
  - better?

- **Lipid Profile**
  - worse?
NRTI’s: TDF/FTC (Truvada)

TDF/FTC (Truvada): evidence supporting renal concerns?

Slow, small magnitude decrement in eGFR over time?

Generalized decrease in renal function
TDF > Other agents; difference small
Modest loss in Y1, less after that
-10 eGFR after 6Y TDF vs -9

Japanese cohort with larger decline in eGFR with TDF vs. ABC

Small risk of proximal tubular toxicity/ Fanconi’s syndrome?

Initial case reports 2002-2004

A known low-level risk; forms the basis of monitoring

Issues: controversial topic
• observational study vs. RCT
• baseline eGFR
• low body weight
• other renal risks
• use of r/PI
• other nephrotoxic meds

Large meta-analysis including RCTs: small difference, perhaps 3-4 mL/min eGFR

Cooper CID 2010

Laprise CID 2013

Nishijima AIDS 2014
NRTI’s: TDF/FTC (Truvada)

TDF/FTC (Truvada): evidence for bone concerns?

- Decrement in bone density after ART initiation
- Then stabilization

- Clinical significance of a 2-4% loss of BMD unclear...
- No apparent evidence that this translates to higher risk of fracture...

ACTG 5202 Study: McComsey, JID, 2011
NRTI’s: TAF/FTC (Descovy)

TAF (tenofovir alafenamide)

Oral TAF prodrug circulates in plasma → TAF taken into cells, hydrolyzed/processed to create tenofovir (TFV), then phosphorylated to create tenofovir-diphosphate (TFV-DP, the active drug) → Plasma concentrations are 90% lower than TDF. Intracellular concentrations much higher.

Virologic non-inferiority to TDF/FTC (data through 144 weeks)

Genvoya (TAF/FTC/cobi/EVG) noninferior to Stribild (TDF/FTC/c/EVG) (Study 104/111):

- at Week 48: 92% VS [TAF] vs. 90% [TDF]
- at Week 96: 87% VS [TAF] vs. 85% [TDF]
- at Week 144, 84.2% [TAF] vs. 80.0% [TDF]

Similar AE profile, lipid effects

Similar data from AMBER Study:

- TAF/FTC/cobi/DRV noninferior to TDF/FTC+cobi/DRV:
  - at Week 48: 91% VS [TAF] vs. 88% [TDF]

Eron JJ et al., AMBER Study: AIDS, 2018

Week 48 data: Sax PE et al., Study 104/111: Lancet, 2015
Week 96 data: Wohl D et al., Study 104/111: JAIDS, 2016
Week 144 data: Arribas J et al., Study 104/111: JAIDS, 2017
**NRTI’s: TAF/FTC (Descovy)**

**Evidence for improved renal profile?**
(Study 104/111 Data through 144 weeks)

- **Less decline in eGFR:**
  - median drop in CrCl:
    - -2.0 mL/min [ECF-TAF]
    - -7.5 mL/min [ECF-TDF] (p<0.001)

- **Fewer discontinuations due to renal dysfunction:**
  - 0 discontinuations [TAF]
  - vs. 12 discontinuations [TDF]

**Similar data from AMBER Study:**
- Less decline in eGFR with DCF/TAF vs. DRV/cobi+TDF/FTC
- Smaller changes in proteinuria

**Also note:**
Can use TAF for patients with eGFR≥30 whereas TDF for patients with eGFR≥60

**Smaller changes in proteinuria by 4 measurements:**
- eGFR, urine prot./creat., RBP/creat., β2M/creat.
NRTI’s: TAF/FTC (Descovy)

Evidence for improved bone profile? → (Study 104/111 Data through 144 weeks)

Less decline in bone density through 96 weeks:

Smaller decrease in **hip** bone density:
-0.7% [ECF-TAF] vs. -3.3% [ECF-TDF] (p<0.001)

Smaller decrease in **spine** bone density:
-1.0% [ECF-TAF] vs. -2.8% [ECF-TDF] (p<0.001)

**Similar data from AMBER Study:**

- Less bone density decline with TAF:

<table>
<thead>
<tr>
<th></th>
<th>Hip</th>
<th>Spine</th>
<th>Fem neck</th>
</tr>
</thead>
<tbody>
<tr>
<td>D/C/F/TAF</td>
<td>+0.21%</td>
<td>-0.68%</td>
<td>-0.26%</td>
</tr>
<tr>
<td>D/C TDF/FTC</td>
<td>-2.73%</td>
<td>-2.38%</td>
<td>-2.97%</td>
</tr>
</tbody>
</table>

Arribas J et al., JAIDS, 2017

Eron JJ et al., AMBER Study: AIDS, 2018
NRTI’s: TAF/FTC (Descovy)

Smaller pill size

- TAF/FTC
- TDF/FTC

Compelling for some patients; less important to other patients

- Stribild
- Genvoya
**NRTI’s:** TAF/FTC (Descovy)

### Lipid profile

Lipid change from baseline to 144 weeks is worse in TAF vs. TDF:

<table>
<thead>
<tr>
<th></th>
<th>TAF</th>
<th>TDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total chol.</td>
<td>↑31</td>
<td>↑13</td>
</tr>
<tr>
<td>HDL</td>
<td>↑6</td>
<td>↑2</td>
</tr>
<tr>
<td>LDL</td>
<td>↑19</td>
<td>↑6</td>
</tr>
<tr>
<td>TG</td>
<td>↑20</td>
<td>↑12</td>
</tr>
</tbody>
</table>

*Note: TDF associated with favorable lipid profile; TAF is a move away from this favorable profile*

### Drug interactions

- **Rifamycins**
  - *Induce* CYP3A4, P-gp, and BRCP
  - *Inhibit* OATP1B1, OATP1B3
  - Net effect of this unknown
  - *Do not co-administer* rifamycins with TAF

- **TAF with cobicistat**
  - TAF a substrate of CYP3A4, P-gp, OATP1B1, and OATP1B3
  - Cobi inhibits these → boosts TAF levels
  - *Thus, TAF dose with cobi is 10mg not 25mg*

*Arribas J et al., JAIDS, 2017*
TAF and TDF Summary

TDF/FTC (Truvada)

Renal Concerns
- Decrease in eGFR over time?
- Risk of tubular toxicity/ Fanconi’s syndrome?

Bone Concerns
- Decrease in bone density?
- Concomitant increase risk of fracture?

TAF/FTC (Descovy)

Renal Profile
better?

Bone Profile
better?

Lipid Profile
worse?

Consider eGFR, proteinuria, osteoporosis, and need for rifamycins in this decision...
NRTI’s: ABC/3TC (Epzicom)

ABC/3TC (Epzicom):

**ABC Hypersensitivity**
- Polymorphism of HLAB57-01 allele
  - 4-8% of overall population positive;
  - 2-4% among African Americans
- ABC binds to HLA molecule, triggering HS reaction

**Cardiovascular Concerns**
- Enhanced platelet reactivity?
- Platelet aggregation?
- Promotes ischemic CV disease?
- Controversial

**Basic biology**
- Theoretical basis for concern
  - Database studies are equivocal
  - Do not clearly demonstrate MI risk

**HLA-B57-01 Testing**
- Fully discriminative
  - If positive → ABC contraindicated
  - If negative → ABC safe

**Guideline Language:** "Increase in CV events is associated with ABC use in some, but not all, cohort studies"

**Issues: controversial topic**
- observational studies vs. RCTs
- other CV risks: accounted for?
- risks from other ARVs?
- duration of follow-up?
- what outcomes assessed?
NRTIs for Patients with HBV

- For Hepatitis B positive patients:
  - TDF/FTC:
    - 2 active agents: good choice
  - TAF/FTC:
    - 2 active agents
    - also FDA approved for HBV+ patients; good choice
  - ABC/3TC:
    - only the 3TC is active
    - if using ABC, typically combine with entecavir
Take Home Points: Summary of NRTI Choices

• TAF vs. TDF:
  – Check current renal function, presence of proteinuria
  – Consider current bone density status
  – Think about drug interactions with TAF

• ABC:
  – Test for HLAB57-01 allele variant
  – Gauge level of cardiovascular risk/concern

• Also:
  – Ascertain Hepatitis B status and factor this into plan
  – Consider tablet size, co-formulation options

• Minor point:
  – Consider lipids
Integrase Inhibitors
Integrase Inhibitors: Overview

• Dominant class of ART: goal is for all patients to be considered for INSTI

• Dolutegravir continues to be in wide use
  – Part of single tablet regimen Triumeq
  – Also available separately

• Bictegravir FDA approved in 2018
  – Only available as part of single tablet Biktarvy

• Elvitegravir (E/C/F/TAF, and E/C/F/TDF)
  – Both Genvoya and Strisild moved from 1st to 2nd line

• Raltegravir remains on 1st line list
Integrase Inhibitor Overview

Dolutegravir (DTG)

- Highly potent, highly efficacious
- High genetic barrier to resistance
- 50mg QD dosing, no booster
- Available as part of Triumeq, or separately
- Need BID if using with EFV, or with rifampin

SINGLE Study: DTG+ABC/3TC vs. EFV/TDF/FTC
- 144-week viral suppression 71% vs. 63% (superior)

SPRING-2 Study: DTG + (ABC/3TC or TDF/FTC) vs. RAL + (ABC/3TC or TDF/FTC)
- 96-week viral suppression 82% vs. 78% (non-inferior)

FLAMINGO Study: DTG+ (ABC/3TC or TDF/FTC) vs. DRV/RTV + (ABC/3TC or TDF/FTC)
- 96-week viral suppression 71% vs. 63% (non-inferior)

Tivicay (DTG 50mg)
Notes/Caution:

- DTG alone only for eGFR>30
- DTG as Triumeq only for eGFR>50
- Inhibits OCT2 \( \rightarrow \) inhibits tubular creatinine secretion, \( \uparrow \)Cr will rise 0.1-0.3

- Decreased absorption when polyvalent cations given (Ca+2, Mg+2, Fe+3, e.g.) \( \rightarrow \) space DTG 2h before or 6h after these

- Caution: boosts metformin levels

- Side effects \( \rightarrow \) discontinuation initially thought to be <2-3% in first year

- Headache, insomnia increasingly recognized

- 15% (85/556) Amsterdam patients stopped DTG:
  - 6% (sleep), 4% (GI), 4% (malaise), 3% (psychological)
  - 2% joint/tendon/muscle, 2% neurologic

- Hypersensitivity/skin reactions uncommon (<1%)

\[\text{Curtis et al., HIV Clin Trials. 2014}\]
\[\text{de Boer et al. AIDS 2016}\]
Integrase Inhibitor Overview (cont’d)

**Bictegravir (BIC)**

- Highly potent, highly efficacious
- High genetic barrier to resistance
- 25mg dose as part of single tablet Biktarvy (TAF/FTC/BIC)
- No booster

**Biktarvy** *(BIC 25mg/TAF 10mg/FTC 200mg)*

**Trial 1489: Biktarvy vs. Triumeq**
- 48-week viral suppression 92% vs 93%
- VS similar in VL<100K, VL 100K-400K and VL>400K

**Trial 1490: Biktarvy vs. TAF/FTC + DTG**
- 48-week viral suppression 89% vs 93%

*Sax PE et al., Lancet, 2017*  
*Gallant, J et al., Lancet, 2017*
Cautions:

- Inhibits tubular secretion of creatinine: raises Cr by 0.1mg/dL
- Only for eGFR>30
- Not for liver disease Child-Pugh C

- Substrate of CYP3A: so any inducer of CYP3A will decrease BIC levels
- Vice versa for inhibitors of CYP3A
- Same for inducer or inhibitor of UGT1A1

- TAF component is a substrate of P-gp and BCRP... so inducers can reduce TAF, inhibitors can increase TAF...

- Do no co-administer with rifampin (reduces BIC and TAF)

- Boosts metformin levels

- Caution for patients with HBV when discontinuing: risk of HBV flare

- Antacids with Al/Mg/Ca: take BIC 2h before
- Fe/Ca supplements: take with BIC and food
Integrase Inhibitors (cont’d)

Elvitegravir (EVG)

- Well-tolerated, strong efficacy
- **150 mg QD** dosing
- Requires cobicistat (150mg QD)
- Lower genetic barrier to resistance
- Hypersensitivity rare
- 1/866 patients had rash in EVG studies

[Images: Stribild (TDF 300/FTC 200/cobi 150/EVG 150) and Genvoya (TAF 10/FTC 200/cobi 150/EVG 150)]

Raltegravir (RAL)

- Very well-tolerated, good potency/efficacy
- **400mg BID** dosing
- Can dose at **1200mg QD** (noninferior to 400mg BID)
- No boosting required
- Lower genetic barrier to resistance
- Hypersensitivity reaction (rare, mild)
- Even rarer: DRESS syndrome

[Images: Isentress (RAL 400 BID) and Isentress HD (RAL 600 x 2 QD)]

Ripamonti et al. AIDS 2014
Integrase Inhibitor Drug Interactions

- There are a lot of these... recommend using interactions website/checker, and consultation with ID specialists to review these
- EVG most problematic because of cobicistat...
- DTG, BIC, RAL are all less problematic...
- Key to remember (and look up): antacids, cations (Mg/Al/Ca), metformin, rifamycins, steroids (dex)

- Screen your patient for these, and good to document (esp. if on EVG) in your notes for others:
  - “patient on INSTI for HIV: consult pharmacy team before starting antacids, anticoagulants, antiepileptics, antidepressives, metformin, rifamycins, cations, or steroids.”
Dolutegravir and Pregnancy

- Dolutegravir in preliminary/emerging data has been associated with low rate of neural tube defects

- Guidelines: “preliminary data suggest that there is an increased risk of neural tube defects (NTDs) in infants born to people who were receiving DTG at the time of conception”
  - “negative pregnancy test result should be documented prior to initiating DTG in antiretroviral therapy (ART)-naive individuals of childbearing potential
  - DTG is not recommended for those who are pregnant and within 12 weeks post-conception
  - DTG is also not recommended for those of childbearing potential who are planning to become pregnant or who are sexually active and not using effective contraception
  - For those who are using effective contraception, use of a DTG-based regimen can be considered after discussing the risks and benefits of this drug with the patient”

- It is not yet known whether other INSTIs pose a similar risk of NTDs (i.e., a class effect).
## Integrase Inhibitor Overview

<table>
<thead>
<tr>
<th></th>
<th>Dolutegravir</th>
<th>Bictegravir</th>
<th>Raltegravir</th>
<th>Elvitegravir</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Frequency</strong></td>
<td>QD (ART-naïve or INSTI-naïve)</td>
<td>QD</td>
<td>1200mg QD or 400mg BID</td>
<td>QD</td>
</tr>
<tr>
<td><strong>BID</strong></td>
<td><strong>BID</strong>: with CYP3A4 or UGT1A1 inducers, or with INSTI mutations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Genetic barrier to resistance</strong></td>
<td>High</td>
<td>High</td>
<td>Lower</td>
<td>Lower</td>
</tr>
<tr>
<td><strong>Single tablet regimen option?</strong></td>
<td>Yes, Triumeq</td>
<td>Yes, Biktarvy</td>
<td>No</td>
<td>Yes, Genvoya or Stribild</td>
</tr>
<tr>
<td><strong>Key side effects</strong></td>
<td>Nausea, diarrhea/GI disturbance, headache, insomnia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increased CK, myositis, hypersensitivity, hepatotoxicity</td>
<td>Myositis, increased CK (4%)</td>
<td>myositis, hypersensitivity, hepatotoxicity, SJS/TEN</td>
<td>hyperlipidemia</td>
</tr>
</tbody>
</table>
Take Home Points: Summary of INSTI Choices

• **Priority:**
  – Consider/prioritize offering an INSTI to all patients ahead of PI or NNRTI based regimen
  – Try to avoid cobicistat boosting where possible

• **DTG:**
  – Daily, well tolerated, best if any history of resistance
  – Part of co-formulated Triumeq
  – Watch developing data on pregnancy

• **BIC:**
  – Daily, well tolerated, no data on patients with resistance

• **Also/always:**
  – Consider drug drug interactions, tablet size
Protease Inhibitors
Protease Inhibitor Overview

• **Darunavir (DRV/r)**
  - Highest potency; fewer side effects than other PIs; well tolerated
  - **800mg QD** dosing (if no DRV mutations)
    – concomitantly administer either RTV 100mg QD or cobicistat 150mg QD
  - **600mg BID** dosing (when DRV mutations present)
    – concomitantly administer RTV 100mg BID (don’t use cobicistat for boosting)

• Side effects: overall low
• As with most PI’s: GI side effects, skin rash (sulfa moiety) – usually self limited, dyslipidemia, rare hepatotoxicity
• Advise take with food

• Unlike ATV: no hyperbilirubinemia; no spacing apart from H2-blockers; PPI’s are ok
• Moved from first line to second line in 2017
• **Darunavir/cobi/TAF/FTC** (800/150/10/200)
  
  – **AMBER** Study (ART-naïve adults, randomized to D/C/F/TAF (n=362) vs. DRV/cobi + FTC/TDF (n=363) to W48 (double blind phase III non-inferiority trial, -10% margin)
  
  – D/C/F/TAF: 91.4% VS at Week 48 vs. DRV/cobi + TDF/FTC: 88.4% VS (+2.7%, 95% CI -1.6% to +7.1%; non-inferior)

  
  – **EMERALD** Ph. 3 switch study (in virally suppressed adults) also showed non-inferior maintenance of VS with D/C/F/TAF vs. control

  
  *AMBER: Eron JJ et al., AIDS, July 2018*

  *EMERALD: Orkin, C et al., Lancet HIV, 2017*
Protease Inhibitors (cont’d)

- **Atazanavir (ATV/r)**
  - Good potency, generally well-tolerated, *300mg QD* (+ RTV 100mg QD)
  - Least effect on lipids of PI’s
  - ↑bilirubin: sometimes cosmetic, sometimes beyond
  - GERD: in ART-naïve patients:
    - H2 blockers: give ATV *400QD* 2h before or 10h after H2; give ATV300/RTV100 anytime
    - PPI: use omeprazole 20 or equivalent (maximum) 12h before ATV
  - Recommend take with food
  - Not in first line recommended list

Recommend against combining ATV with PPI
Take Home Points: Summary of PI Choices

- **Priorities:**
  - As noted earlier, prioritize PIs below/after INSTIs in most/all patients
  - With ritonavir or cobicistat booster, must carefully check all drug interactions

- **Darunavir:**
  - Daily (for most patients), well tolerated
  - Part of co-formulated Symtuza

- **Atazanavir, Lopinavir, others:**
  - Older, and most patients should be modernized away from these

- **Also/always:**
  - Consider drug drug interactions, tablet sizes
<table>
<thead>
<tr>
<th>NNRTI Overview</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rilpivirine (RPV)</strong></td>
<td><strong>Doravirine (DOR)</strong></td>
</tr>
<tr>
<td>• Potency similar to EFV</td>
<td>• FDA approved 2018: ART-naïve</td>
</tr>
<tr>
<td>• Lacks CNS side effects</td>
<td>• Good potency</td>
</tr>
<tr>
<td>• Less lipid effects</td>
<td>• Has TDF in combination pill</td>
</tr>
<tr>
<td><strong>Edurant: RPV 25</strong></td>
<td><strong>Pifeltro: DOR 100</strong></td>
</tr>
<tr>
<td><strong>Odefsey: RPV 25/ TDF 25/FTC 200</strong></td>
<td><strong>Pifeltro: No dose adjustment for renal failure or liver disease</strong></td>
</tr>
<tr>
<td><strong>Odefsey: RPV 25/ TDF 25/FTC 200</strong></td>
<td><strong>Delstrigo: only for eGFR&gt;50</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Delstrigo: DOR 100/ TDF 300/FTC 300</strong></td>
</tr>
<tr>
<td>• Lower efficacy when VL&gt;100K or CD4&lt;200</td>
<td>• Low rates of headache, nausea, diarrhea</td>
</tr>
<tr>
<td>• Requires 400 cal. meal</td>
<td>• Metabolized by CYP3A;</td>
</tr>
<tr>
<td>• H2 blocker: give 12h before or 4h after RPV</td>
<td>• Don’t combine with rifampin (rifabutin ok if use DOR 100 BID)</td>
</tr>
<tr>
<td>• PPI: avoid</td>
<td>• In second line list</td>
</tr>
<tr>
<td>• In second line list</td>
<td></td>
</tr>
</tbody>
</table>
### NNRTI Overview (cont’d)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Potency</th>
<th>Dosage</th>
<th>Side Effects</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efavirenz</strong> (EFV)</td>
<td>Potency well established</td>
<td>QD</td>
<td>Caution with depression, Rare suicidality, CNS side effects: insomnia, dreams</td>
<td>In second line list</td>
</tr>
<tr>
<td><strong>Etravirine</strong> (ETV)</td>
<td>Potency similar to EFV</td>
<td>Less lipid effects</td>
<td>BID drug (200mg BID) (data support 400mg QD)</td>
<td>In second line list</td>
</tr>
</tbody>
</table>
Take Home Points: Summary of NNRTI Choices

• **Priorities:**
  – As noted earlier, prioritize NNRTIs below/after INSTIs in most/all patients
  – Lower genetic barrier to resistance

• **Efavirenz:**
  – Older med; should modernize regimen in most patients

• **Rilpivirine:**
  – Part of co-formulated Odefsey; calorie requirement, and some drug interactions

• **Etravirine, Doravirine:**
  – Can make sense in certain situations
Single Tablet Regimens
Single Tablet Co-Formulations

NRTI
- Emtricitabine
- Lamivudine
- Abacavir

NNRTI
- Efavirenz
- Rilpivirine

Protease
- Tenofovir
- Ritonavir
- Atazanavir
- Darunavir
- Cobicistat
- Bictegravir
- Raltegravir

INSTI
- TAF
- Descovy
- Evotaz
- Prezcobix
- Epzicom
- Truvada

Elvitegravir
- Descovy
- April, 2016
- January, 2015
- January, 2015

Dolutegravir
- Dolutegravir
- April, 2016
- January, 2015

Doravirine

Efavirenz

Roflumilast

April, 2016

2004
Single Tablet Regimens

NRTI
- Emtricitabine
- Lamivudine
- Abacavir
- Tenofovir

NNRTI
- Efavirenz
- Rilpivirine

INSTI
- Bictegravir

Protease
- Ritonavir
- Atazanavir
- Darunavir
- Cobicistat
- Raltegravir
- Elvitegravir
- Dolutegravir

Complera

August, 2011
Single Tablet Regimens

- **NRTI**
  - Emtricitabine
  - Lamivudine
  - Abacavir

- **NNRTI**
  - Efavirenz
  - Rilpivirine

- **Protease**
  - Tenofovir
  - Ritonavir
  - Atazanavir
  - Darunavir
  - Cobicistat

- **INSTI**
  - Raltegravir
  - Elvitegravir
  - Bictegravir

- **Combination**
  - Stribild

August, 2012

Dolutegravir

Single Tablet Regimens

- **NRTI**: Emtricitabine
  - Tenofovir
  - TAF
  - Ritonavir
  - Atazanavir
  - Darunavir
  - Cobicistat

- **NNRTI**: Abacavir
  - Lamivudine
  - Doravirine
  - Efavirenz
  - Rilpivirine
  - Dolutegravir
  - Elvitegravir

- **Protease**: Bictegravir
- **INSTI**: Raltegravir
  - Bictegravir
  - Dolutegravir
  - Elvitegravir

*August, 2014*
Single Tablet Regimens

- Emtricitabine (NRTI)
- Lamivudine (NRTI)
- Abacavir (NRTI)
- Efavirenz (NNRTI)
- Rilpivirine (NNRTI)
- Tenofovir (NRTI)
- TAF
- Ritonavir (Protease)
- Atazanavir (Protease)
- Cobicistat
- Darunavir (Protease)
- Raltegravir (INSTI)
- Elvitegravir (INSTI)
- Biktarvy

February, 2018
Single Tablet Regimens

NRTI
- Emtricitabine
- Tenofovir
- TAF
- Lamivudine
- Abacavir

NNRTI
- Efavirenz
- Rilpivirine
- Efavirenz

Protease
- Ritonavir
- Atazanavir
- Darunavir
- Cobicistat

INSTI
- Bictegravir
- Elvitegravir
- Raltegravir

Symtuza

July, 2018

8121
Single Tablet Regimens

NRTI
- Emtricitabine
- Lamivudine
- Abacavir
- Tenofovir
- TAF
- Rilpivirine
- Efavirenz
- Ritonavir
- Atazanavir
- Darunavir
- Cobicistat
- Raltegravir
- Elvitegravir
- Bictegravir
- Dolutegravir

NNRTI
- Delstrigo
- Doravirine

INSTI
- August, 2018

Protease
Take Home Points: Co-Formulated Tablets

• **Advances:**
  – There are now several highly potent well tolerated single tablet regimens
  – Try to see if pill burden can be reduced by using a single tablet regimen

• **Caution:**
  – If new drug interactions arise, especially during an inpatient hospitalization, may be easy to overlook the need to disaggregate the meds or shift to another option
## U.S. DHHS Guideline Update: October, 2018

### Initial Regimens “for Most People”

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BIC/TAF/FTC</strong></td>
<td>* If reproductive potential, consult guidance</td>
</tr>
<tr>
<td><strong>DTG/ABC/3TC</strong></td>
<td>Only if HLB57-01 negative</td>
</tr>
<tr>
<td><strong>RAL + (TDF/FTC or TAF/FTC)</strong></td>
<td>* If reproductive potential, consult guidance</td>
</tr>
</tbody>
</table>

### Initial Regimens “in Certain Clinical Situations”

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EVG/cobi + (TDF/FTC or TAF/FTC)</strong></td>
<td>* If reproductive potential, consult guidance</td>
</tr>
<tr>
<td><strong>RAL/ABC/3TC</strong></td>
<td>Only if HLAB57 negative and VL&lt;100,000</td>
</tr>
<tr>
<td><strong>(DRV/RTV or DRV/cobi) + (TDF/FTC or TAF/FTC)</strong></td>
<td>* If reproductive potential, consult guidance</td>
</tr>
<tr>
<td><strong>(DRV/cobi or DRV/RTV) + ABC/3TC</strong></td>
<td>Only if HLB57-01 negative</td>
</tr>
<tr>
<td><strong>(ATV/cobi or ATV/RTV) + (TDF/FTC or TAF/FTC)</strong></td>
<td>Only if HLAB57 negative and VL&lt;100,000</td>
</tr>
<tr>
<td><strong>DOR/TDF/FTC or (DOR + TAF/FTC)</strong></td>
<td>Only if VL&lt;100,000 &amp; CD4+ &gt;200</td>
</tr>
</tbody>
</table>

### Organizational comments:

- BIC/TAF/FTC new in 2018...
- DRV moved out of first line list in 2017...
- EVG/cobi/TAF/FTC and EVG/cobi/TDF/FTC moved out of first line in 2018...
- Guidelines don’t really emphasize TAF vs. TDF much...

Adapted from: US DHHS ART Guidelines – October 28, 2018 Update
Case 1

51 year old man registering for care. VL = 41,000, CD4+ count = 682. Creatinine = 1.4, and eGFR = 55 mL/min. LDL = 68. HLAB57-01 is negative. No other medical problems. Which regimen(s) would you offer?

A) TAF/FTC/BIC (Biktarvy)
B) TAF/FTC (Descovy) + DTG (Tivicay)
C) ABC/3TC/DTG (Triumeq)
D) TDF/FTC (Truvada) + RTV/DRV
E) EVG/cobi/TAF/FTC (Genvoya)
F) RAL + TAF/FTC (Descovy)
• 51 year old man registering for care. VL = 41,000, CD4+ count = 682. Creatinine = 1.4, and eGFR = 55 mL/min. LDL = 68. HLAB57-01 is negative. No other medical problems. Which regimen(s) would you offer?

• A) TDF/FTC (Truvada) + DTG (Tivicay) ➔ eGFR is <60: avoid TDF.
• B) TAF/FTC (Descovy) + DTG (Tivicay) ➔ Fine choice.
• C) ABC/3TC/DTG (Triumeq) ➔ Fine choice.
  – B57 negative, thus eligible. No major CV concerns. Triumeq for eGFR>50.
• D) TDF/FTC (Truvada) + RTV/DRV ➔ eGFR is <60: would avoid TDF, and especially in combination with RTV/PI, which boosts TDF. Also, second line.
• E) EVG/cobi/TAF/FTC (Genvoya) ➔ eligible since GFR is >30, but favor unboosted INSTI instead of using cobi. Also, second line.
• F) RAL + TAF/FTC (Descovy) ➔ Fine, but prefer potency/genetic barrier of DTG or BIC.
Case 2

- Same patient as Case 1, but lower eGFR:
- 51 year old man registering for care. VL = 41,000, CD4+ count = 682. Creatinine = 1.6, and eGFR = 31 mL/min. LDL = 68. HLAB57-01 is negative. No other medical problems. Which regimen would you offer?

- A) TDF/FTC (Truvada) + DTG
- B) TAF/FTC (Descovy) + DTG
- C) TAF/FTC/BIC (Biktarvy)
- ABC/3TC/DTG (Triumeq)
- D) TDF/FTC + RTV/DRV
- E) EVG/cobi/TAF/FTC (Genvoya)
- F) TAF/FTC (Descovy) + RAL 1200 QD
Case 2

- 51 year old man registering for care. VL = 41,000, CD4+ count = 682. Creatinine = 1.6, and eGFR = 31 mL/min. LDL = 68. HLAB57-01 is negative. No other medical problems. Which regimen would you offer?

- A) TDF/FTC (Truvada) + DTG → eGFR is <60: avoid TDF
- B) TAF/FTC (Descovy) + DTG → eGFR is >30: fine choice; monitor.
- C) TAF/FTC/BIC (Biktarvy) → eGFR is >30: fine choice; monitor.
- D) ABC/3TC/DTG (Triumeq)
  - B57 negative: eligible. Some CV concerns with renal disease.
  - But Triumeq is only for eGFR>50.
- D) TDF/FTC + RTV/DRV → eGFR is <60: avoid TDF, esp. with RTV/PI.
- E) EVG/cobi/TAF/FTC (Genvoya) → Since eGFR<70, favor unboosted INSTI
- F) TAF/FTC (Descovy) + RAL 1200 QD → Fine choice at eGFR>30, but lower barrier to resistance, and 3 pills where single tablet is possible
Case 3

- 48 y.o. man, newly diagnosed last month, VL 105,000, CD4+ count = 487. Has history of hyperlipidemia (LDL = 140, Total cholesterol = 221), smokes 10 cigarettes/day, and has HBA1c = 7.1%. BUN/creatinine 14/1.2, eGFR=73 mL/min, UA: 1+ protein. Which ART is optimal?

- A) TAF/FTC (Descovy) + DTG
- B) TDF/FTC (Truvada) + DTG
- C) TAF/FTC/BIC (Biktarvy)
- D) ABC/3TC/DTG (Triumeq)
- E) TAF/FTC (Descovy) + RTV/DRV
- F) TDF/FTC/DOR (Delstrigo)
Case 3

- **A)** TDF/FTC (Truvada) + DTG
  - eGFR>60 is ok, but with 1+ proteinuria, favor TAF over TDF
- **B)** TAF/FTC (Descovy) + DTG
  - OK choice, eGFR>30, but already has proteinuria...
- **C)** TAF/FTC/BIC (Biktarvy)
  - OK choice, eGFR>30, but already has proteinuria...
- **D)** ABC/3TC/DTG (Triumeq)
  - OK choice, eGFR>50; but with CV risk factors (lipids/smoking/DM), balance CV risk with ABC vs. using TAF in patient with proteinuria
- **E)** TAF/FTC + RTV/DRV
  - With cardiac and renal risk factors, avoid PI if possible. Second line.
- **F)** TDF/FTC/DOR (Delstrigo)
  - With proteinuria, avoid TDF. Second line.

48 y.o. man, newly diagnosed, VL 105,000, CD4+ = 487. Has hyperlipidemia (LDL = 140, Total cholesterol = 221), smokes 10 cigarettes/day, HBA1c = 7.1%, BUN/creatinine 14/1.2, eGFR=73 mL/min, UA: 1+ protein. Which ART is optimal?
Case 4

- 34 y.o. woman, VL 23,000, CD4+ 610. Has chronic HBV: HBsAg+ HBsAb+ HBcAb+ HBV DNA = 6M IU/mL. HLAB57-01 negative. eGFR=90. Which regimen(s) would you offer?

- A) TAF/FTC (Descovy) + DTG
- B) TDF/FTC (Truvada) + DTG
- C) TAF/FTC/BIC (Biktarvy)
- D) ABC/3TC/DTG (Triumeq)
- E) TDF/FTC (Truvada) + RTV/DRV
- F) ABC/3TC (Epzicom) + RAL
Case 4

• 34 y.o. woman, HIV VL 123,000, CD4+ 610. Has chronic HBV: HBsAg+ HBsAb+ HBcAb+ HBV DNA+. HLAB57-01 negative. eGFR=90. Which regimen(s) would you offer?

• A) TAF/FTC (Descovy) + DTG → fine choice
• B) TDF/FTC (Truvada) + DTG → fine choice
• C) TAF/FTC/BIC (Biktarvy) → fine choice
• D) ABC/3TC/DTG (Triumeq) → 3TC alone: would add entecavir
• E) TDF/FTC (Truvada) + RTV/DRV → OK, but prefer integrase > PI
• F) ABC/3TC (Epzicom) + RAL → Combo is second line, not for HIV VL>100K (always check), would need to add entecavir with 3TC, and would prefer integrase over PI
Case 5

- 57 y.o. woman, VL=14K, CD4=390. DM2: A1c=8.0%, takes metformin at maximum 875mg TID dose + glipizide 5mg BID, eGFR=90, UA with no protein. HLAB57 negative. Which ART regimen do you favor?

- A) TAF/FTC (Descovy) + DTG
- B) TDF/FTC (Truvada) + DTG
- C) TAF/FTC/BIC (Biktarvy)
- D) ABC/3TC/DTG (Triumeq)
- E) TDF/FTC/cobi/EVG (Stribild)
- F) TAF/FTC (Truvada) + RAL
Case 5

- 57 y.o. woman, VL=14K, CD4=390. DM2: A1c=8.0%, takes metformin at maximum 850mg TID dose + glipizide 5mg BID, eGFR=90, UA with no protein. HLAB57 negative. Which ART regimen do you favor?

<table>
<thead>
<tr>
<th>Option</th>
<th>Notes</th>
</tr>
</thead>
</table>
| A) TDF/FTC (Truvada) + DTG | - Potentially ok; potentially not  
- DTG boosts metformin → would need close monitoring as already on max dose (but might be ok)  
- If need to reduce metformin, might have to add 2nd med, or DM2 control may get worse |
| B) TAF/FTC (Descovy) + DTG | - Same as choice A |
| C) TAF/FTC/BIC (Biktarvy) | - Same as choice A |
| D) ABC/3TC/DTG (Triumeq) | - Same as choice A |
| E) TDF/FTC/cobi/EVG (Stribild) | - eGFR>70, no DDI* → fine choice,  
- but prefer to avoid cobicistat if RAL possible |
| F) TAF/FTC (Truvada) + RAL | - eGFR>30, no DDI* → fine choice  
- Balance your view of RAL vs. DTG/BIC against DM control |
What about “2-Drug Therapy” for Initiation?

- **Dolutegravir/rilpivirine (Juluca)**
  - FDA approved 11/21/17 for *maintenance* for HIV therapy (i.e., switch of therapy in a virally suppressed patient)
  - **SWORD-1 & SWORD-2** Phase III switch studies: DTG/RPV 95% VS @ W48 vs. Control: 95% VS, difference -0.2% (-3.0 — +2.5%)
  - Data on *ART-naive* patients not yet available...

  *Lilbre JM. et al, Lancet, March 2018*

- **Dolutegravir/3TC**
  - **GEMINI-1 & GEMINI-2**: DTG/3TC vs. DTG/TDF/FTC in ART-naïve patients
  - Week 48 viral suppression 91% (DTG/3TC) vs 93% (DTG/TDF/FTC)

  *Cahn P. et al, Lancet, November 2018*
Take Home Principles

- **Choosing the NRTI backbone:**
  - Consider TDF vs. TAF
    - Assess eGFR, proteinuria, osteoporosis, importance of pill size
  - Consider ABC vs. TDF/TAF
    - Need HLAB57-01 test. Assess question/opinion of cardiac risk issues
  - Consult with experts when all NRTI’s seem problematic

- **Goal is to use INSTI in most patients unless other issues prevail**
  - Consider prior history, drug intolerance, side effect, desire for single-tablet regimen, drug interactions
  - Consider DTG, BIC for most patients if possible

- **Assess PI and NNRTI possibilities if needed:**
  - Consider dosing (QD vs. BID), desire for single tablet regimen, psychiatric history, lipid profile, GI issues, renal status, likelihood of strong adherence/genetic barrier
  - Assess baseline VL and CD4 count

- **Focus on DHHS first-line recommended regimens**


References (2)


References (3)


Thank You!

• Happy to take any questions!

• For questions after the conference:
  – vivek.jain@ucsf.edu – please email me anytime