Annual HIV 2019 Update

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CPE Information

• Target Audience: Pharmacists and Pharmacy Technicians
• ACPE#: 0202-0000-19-082-02-P/T
• Activity Type: Knowledge-based
Supporter

This activity is supported by an independent educational grant from Gilead Sciences, Inc., Merck Sharp, and Dohme Corporation.
Learning Objectives

At the completion of this knowledge-based activity, participants will be able to:

• Identify important changes in recently updated guidelines that have the potential to influence the management of HIV/AIDS.

• Describe clinically important drug updates, adverse effects, and drug-drug interactions associated with new drug classes used in the management of HIV/AIDS and common comorbidities.

• Outline strategies for improving adherence to drug therapy in patients with HIV/AIDS.
1. Which of the following ARV regimens has been removed from current Antiretroviral Guidelines as an appropriate initial regimen for PLWH (persons living with HIV)?

A. ABC/3TC/dolutegravir (Triumeq)
B. TAF/FTC/bictegravir (Biktarvy)
C. TAF/FTC/Elvitegravir/cobi (Genvoya)
D. TDF/3TC/doravirine (Delstrigo)
E. DTG plus lamivudine
2. Which of the following has been recently associated with the use of integrase inhibitor based therapy?

A. Dyslipidemia
B. Lactic acidosis
C. Myocardial infarction
D. Weight gain
3. Which of the following might occur when changing from a ritonavir boosted darunavir regimen to Symtuza (cobicistat boosted darunavir regimen)?

A. No differences expected since ritonavir equal to cobicistat.
B. Increased risk of CYP3A induction interactions
C. Higher levels of DRV are expected with cobicistat boosting
D. Increased risk of CYP3A 2B6, 2C9, and 2C19 inhibition.
4. Which of the following prophylaxis is no longer recommended in a person with AIDS, VL of 100K c/ml, and CD4 35 cells/mm3, who is starting ART?

A. PCP
B. CMV
C. Toxo
D. MAC
**Glossary**

- ARV = antiretroviral agent
- ART = antiretroviral therapy
- UD VL = undetectable HIV RNA
- NRTI = nucleoside reverse transcriptase inhibitor
- PI = Protease inhibitor
- NNRTI = non nucleoside reverse transcriptase inhibitor
- INSTI = integrase inhibitor
- /cobi = cobicistat
- /r = ritonavir
- FTC = emtricitabine
- 3TC = lamivudine

- TDF = tenofovir disoproxil fumarate
- TAF = tenofovir alafenamide
- ABC = abacavir
- DRV/r = darunavir/ritonavir
- ATV/r = atazanavir/ritonavir
- RPV = rilpivirine
- DOR = doravirine
- BIC = bicitravir
- DTG = dolutegravir
- RAL = raltegravir
- EVG/c = elvitegravir/cobicistat
- IBA = ibalizumab
TOP TEN+ “HOT” Topics

• State of the HIV Epidemic
• New ART formulations in 2018
• Is 2 ARVs as Good as 3
• ART Guidelines for treatment naïve PLHIV
• Ritonavir vs cobicistat drug interactions
• Switching/Simplification of regimens
• Selected Updates in Pregnancy
• PrEP Updates: TDF vs TAF (Discover)
• New ARVs in the Pipeline and HIV Cure
• Adherence
• 36.9 million living with HIV (1.2 PLWH in the US).
• 21.7 million receiving ART (60% US with UD VL)
• 1.8 million newly HIV infected (38 million in the US)
• New HIV infections reduced by 47% since the peak in 1996
• 77.3 million HIV infected since the epidemic started
• 35.4 million deaths from AIDS-related illnesses since the epidemic began.
• AIDS-related deaths reduced by more than 51% since the peak in 2004.
• Goal: to end HIV transmission and control the HIV epidemic by 2030

Trends in Age-Adjusted Annual Rates of Death due to HIV, 1985–2016—United States

Note. For comparison with data for 1999 and later years, data for 1987–1998 were modified to account for ICD-10 rules instead of ICD-9 rules.
Estimated Annual US HIV Infections

Estimated annual HIV infections in the U.S. declined **18%**

Between 2008 - 2014 infections fell from 45,700 to 37,600

- **56%** decline among people who inject drugs
- **36%** decline among heterosexuals
- **26%** decline among gay and bisexual men aged 35-44 years
- **18%** decline among gay and bisexual men aged 13-24 years

Gay and bisexual men remain most affected

- 2014: 37,600 New HIV Infections
- 2014: 26,200 infections
- 2014: 5% who inject drugs
- 2014: 70%

New HIV Diagnoses in the US 2017 for the Most-Affected Subpopulations

- Black, Male-to-Male Sexual Contact: 9,807
- Hispanic/Latino, Male-to-Male Sexual Contact: 7,436
- White, Male-to-Male Sexual Contact: 6,982
- Black Women, Heterosexual Contact: 4,008
- Hispanic/Latina Women, Heterosexual Contact: 1,717
- White Women, Heterosexual Contact: 1,058
- 25% decline in AA women and 20% in Hispanics/Latinos

Diagnoses of US HIV Infection among Adults and Adolescents by Age 2017

Note. Data for the year 2016 are considered preliminary and based on 6 months reporting delay.
About 50% are PLWH; estimates of 70% by 2020

17% (6,812) of 39,782 new HIV dx in 2016; 43% in those 50-54 yrs old

Older persons are less likely to get tested; HIV signs/sx mistaken for aches and pains of normal aging

49% aged 60+ yrs, 2x more likely w/ AIDS illness or CD4 <200 c/mm3 vs 21% <40 yrs old (VACS)
  - Shingles 7% increase vs 3% < 40 yrs
  - Bacterial pneumonia: 6 fold increase
  - Anemia, thrombocytopenia

Routine HIV screening recommended for older persons

Rates of Adults and Adolescents Living with HIV Infection 2016—US and 6 Dependent Areas

N = 1,006,691   Total Rate = 367.6

Note. Data are based on address of residence as of December 31, 2016 (i.e., most recent known address).
Goals of Antiretroviral Therapy

- Achieve undetectable (UD) HIV VL
- Restore and/or preserve immune function (eg, ↑CD4 count)
- Reduce HIV-associated inflammation and non-HIV-related mortality and morbidity
- Reduce OI, progression to AIDS (CD4 <200 or OI), non-AIDS-related illnesses
- Prevent transmission of HIV
- Improvement in quality of life

# HIV Transmission Risk with Undetectable HIV Viral Load

<table>
<thead>
<tr>
<th>Trial</th>
<th>Subjects</th>
<th>Outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPTN 052 (RC) 5.5 yr F/U</td>
<td>1763 heterosexual discordant couples early vs delayed ART</td>
<td>HIV incidence 0.9%</td>
<td>96.4% protection, 8 linked HIV infections 36% unlinked (p&lt;0.0001)</td>
</tr>
<tr>
<td>Partners 1 (F/U 1.3 yr)</td>
<td>1166 discordant heterosexual/MSM couples</td>
<td>58,000 condomless acts.</td>
<td>No HIV linked infections 11 unlinked infections (10 MSM, 1 heterosexual)</td>
</tr>
<tr>
<td>Partners 2 Observational</td>
<td>783 MSM discordant couples</td>
<td>77,000 condomless acts.</td>
<td>No HIV linked infections</td>
</tr>
<tr>
<td>Opposites Attract Study</td>
<td>343 MSM discordant couples 1.5 yr/couple F/U</td>
<td>16,800 condomless acts.</td>
<td>No HIV linked infections; 3 unlinked HIV infections</td>
</tr>
<tr>
<td>Partners PrEP</td>
<td>4747 heterosexual HIV discordant couples</td>
<td>HIV incidence 2.08/100py before ART 1.79/100 py 0-6 mo ART 00/100 py &gt; 6 mo ART</td>
<td>No HIV infections &gt; 6 months of ART to achieve VL suppression</td>
</tr>
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</table>

What are the Current Recommendations for Antiretroviral Therapy (ART)

https://aidsinfo.nih.gov/understanding-hiv-aids/infographics
• ART is recommended for all individuals with HIV
  • Regardless of CD4 T lymphocyte cell count
  • Regardless of viral load (e.g. elite controllers and low level viremia)
  • Willingness and readiness to initiate therapy.
  • May be deferred b/c clinical and/or psychosocial factors, but should be initiated ASAP

• Baseline Labs
  • Genotype, CD4, HIV VL, HLAB5701, G6PD, Toxo
  • Renal and liver function
  • HAV, HBV, HCV serology

• When to Start ART?

2018 DHHS and IAS Guidelines Initial Basic ART Regimen

2 NRTI (The “nuc” backbone) PLUS EITHER

1 NNRTI ("NNRTI based regimen")

A boosted protease inhibitor ("PI based regimen")

1 integrase inhibitor ("INSTI based" regimen)
Considerations for Selecting The Initial ART Regimen

- Resistance Testing
- Co-morbid Conditions (e.g. Hepatitis CV Disease, Mental illness)
- Potency
- Drug Interactions
- Lifestyle Adherence Dosing Pill Burden Preference
- Toxicity Short Term Long Term

Initial ART Treatment
Case Discussion

JM is a 35 year old female who just found out about her positive HIV test results. She reports she is ready and motivated to start ART but prefers a once daily regimen. Risk factors include her HIV-infected husband who is just starting ART.

PMH:
- Diabetes on metformin 500 mg bid
- Hypertension on amlodipine 10 mg daily
- CHF s/p MI on carvedilol 25 mg bid, losartan 100 mg daily, furosemide 80 mg bid

Labs:
- CD4 344 c/mm³
- HIV VL 69,000 c/ml
- AST/ALT/BUN/Scr WNL
- HbsAG neg, HBsAB pos
- LDL 100 mg/dl
- HDL 60 mg/dl
- A1c 7.1%
- HIV Genotype pending
- HLA B5701 Pending
## New ARVs FDA approved in 2018

<table>
<thead>
<tr>
<th>ARVs</th>
<th>FDA Approval</th>
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<tbody>
<tr>
<td>Bictegravir/TAF /FTC (Biktarvy)</td>
<td>Feb 2018</td>
</tr>
<tr>
<td>Ibalizumab (Trogarzo)</td>
<td>March 2018</td>
</tr>
<tr>
<td>Darunavir/cobicistat/FTC/TAF (Symtuza)</td>
<td>July 2018</td>
</tr>
<tr>
<td>Doravirine (Pifeltro)</td>
<td>August 2018</td>
</tr>
<tr>
<td>Doravirine 100 mg/3TC 300 mg/TDF 300 mg (Delstrigo)</td>
<td>August 2018</td>
</tr>
</tbody>
</table>
Which is the initial recommended ARV for Treatment Naïve PLWH (JM) per ARV Guidelines?

A. ABC/3TC/dolutegravir (Triumeq)
B. TAF/FTC/bictegravir (Biktarvy)
C. TAF/FTC/Elvitegravir/cobi (Genvoya)
D. TAF/FTC/darunavir/cobi (Symtuza)
E. TDF/3TC/Doravirine (Delstrigo)
F. TAF/FTC plus ibalizumab (Trogarzo)

PMH: DM, HTN, CHF s/p MI
Meds: amlodipine, furosemide, carvedilol, losartan, metformin
Labs: CD4 544 c/mm³    HIV VL 69,000 c/ml    A1C 7.1%
      AST/ALT/BUN/Scr WNL     HbsAG neg, HBsAB positive
      LDL 100 mg/dl/HDL 60    HIV Genotype and HLA B5701 pending
Selecting the NRTIs ("Nuc") Backbone for the ARV Regimen

- Zidovudine, stavudine, didanosine not recommended
- Emtricitabine (FTC) = lamivudine (3TC)
- Abacavir (ABC) Pros:
  - No adjustments in renal dysfunction
  - Well tolerated if HLA-B*5701 neg
  - FDC with lamivudine (Epzicom)
  - FDC with dolutegravir (Triumeq)
- ABC Cons:
  - Less effective if HIV VL >100K (except with INSTIs)
  - Concern about CV morbidity/mortality
  - Need for HLA-B*5701 testing
  - No anti-HBV activity
  - C/I Child Pugh B/C; ↓200 mg bid Childs Pugh A (↑AUC 89%, ↑t1/2 58%).

# Selecting NRTIs (“nucs”): Comparing Tenofovir DF to TAF

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>TAF (Tenofovir alafenamide)</th>
<th>TDF (Tenofovir disoproxil fumarate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-HBV activity</td>
<td>✓</td>
<td>✔</td>
</tr>
<tr>
<td>Lipid lowering</td>
<td>Neutral</td>
<td>✔</td>
</tr>
<tr>
<td>Use in renal dysfunction</td>
<td>CrCl &gt; 30cc/min</td>
<td>CrCl &gt; 50-60cc/min</td>
</tr>
<tr>
<td>Renal toxicity</td>
<td>Less</td>
<td>Yes</td>
</tr>
<tr>
<td>Reduced BMD</td>
<td>Less</td>
<td>Yes</td>
</tr>
<tr>
<td>FDC formulation</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>ART Efficacy</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>PrEP/PEP Use</td>
<td>✓PrEP, ? PEP</td>
<td>✔</td>
</tr>
</tbody>
</table>

Descovy package insert; Corado KC & Daar ES. Expert Opin Pharmacother 2017:18:4, 427; Hare B et al. CROI 2019, Abst 104LB
**Doravirine 100mg (DOR, Pifeltro)**

- NNRTI approved August 2018 for treatment naïve persons
- FDC: TDF 300 mg/300 mg 3TC/DOR 100 mg (Delstrigo)
- Pharmacokinetics
  - Rapid absorption; peak concentrations in a median of 1–4 h
  - T1/2 = 15 hr
  - No dosage adjustment in renal or mild/mod liver dysfunction (C/P A/B).
- Dosage: Administer with or without food once daily
  - If administered with rifabutin: One tablet BID (approx 12 hrs apart)
  - Avoid if CrCL <50 cc/min (d/t TDF/3TC component)

• CYP3A4 substrate
  • C/I with strong CYP3A enzyme inducers d/t decreased efficacy (e.g. anticonvulsants, rifampin, rifabutin, rifapentine, enzalutamide, mitotaine, St. John’s wort)
  • Ritonavir will increase DOR levels
• No CYP1A2, 2B6 or 3A4 inhibition, induction, or effect on transporters (eg. Pgp, OATP1B1,B3, OAT1,3 OCT2, MATE, BSEP)
• Monitor for immune reconstitution syndrome
• Side effects counseling: nausea, headache, fatigue, diarrhea, dizziness, abnormal dreams, rash

**DRIVE-AHEAD: DOR/3TC/TDF vs EFV/FTC/TDF VL Outcomes @ 48,96 Wks and Wk 48 Adverse Effects**

- MC, R, DB phase III non-inferiority trial (n=728)
- Treatment-naive adults with HIV-1 RNA ≥ 1000 copies/mL and no drug resistance
- NS in baseline HIV RNA> or <100K c/ml

### Analysis Results

#### 48 to 96 weeks Treatment difference:
3.5 to 3.8% (95% CI: -2.4% to 10.0%)

<table>
<thead>
<tr>
<th>AEs, % (n) @ 48 wks</th>
<th>DOR/3TC/TDF (n = 364)</th>
<th>EFV/FTC/TDF (n = 364)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>8.8</td>
<td>37.1</td>
</tr>
<tr>
<td>Headache</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Sleep disturbances</td>
<td>12.1</td>
<td>25.5</td>
</tr>
<tr>
<td>Insomnia</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Depression and suicide/self-injury</td>
<td>4.1</td>
<td>6.6</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>17</td>
<td>34</td>
</tr>
<tr>
<td>Nausea</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Rash</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>Any drug related AE</td>
<td>32 (116)</td>
<td>65 (236)</td>
</tr>
<tr>
<td>AE leading to d/c</td>
<td>2 (11)</td>
<td>7 (27)</td>
</tr>
</tbody>
</table>

DRIVE-FORWARD: 2 NRTIs + Either DOR or DRV/RTV in Adult PLWH

- MC, R, DB, phase III study (n=766) no drug resistance
- Treatment naive adults HIV VL >1000 c/ml;

766 adults HIV-1 RNA ≥ 1000 c/mL,

**Virologic Outcomes at Wks 48 and 96**

<table>
<thead>
<tr>
<th>Wk 48</th>
<th>48 wks</th>
<th>96 wks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doravirine 100 mg QD + 2 NRTIs* + DRV/RTV Placebo (n = 383)</td>
<td>80</td>
<td>73.1</td>
</tr>
<tr>
<td>DRV/RTV 800/100 mg QD + 2 NRTIs* + Doravirine Placebo (n = 383)</td>
<td>84</td>
<td>66</td>
</tr>
</tbody>
</table>

*Open-label extension for 96 wks*

Treatment difference:
- 3.9% (95% CI -1.6 to 9.4%)
- 7.1% (95% CI: 0.5% to 13.7%)

**DRIVE-FORWARD: Safety at Wks 96**

- AEs occur in approx. 1/3 of pts in both groups
- Most occurred before Wk 48; no AE caused > 3 d/c in either arm.
- Grade 2 bilirubin elevation: DOR, 1.8%; DRV/RTV, 0.3%

<table>
<thead>
<tr>
<th>AE, n (%)</th>
<th>DOR (n = 383)</th>
<th>DRV/RTV (n = 383)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug related ADRs</td>
<td>123 (32)</td>
<td>123 (32)</td>
</tr>
<tr>
<td>AE in &gt; 10% in ≥ 1 arm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>65 (17.0)</td>
<td>91 (23.8)</td>
</tr>
<tr>
<td>Nausea</td>
<td>45 (11.7)</td>
<td>52 (13.6)</td>
</tr>
<tr>
<td>Headache</td>
<td>57 (14.9)</td>
<td>46 (12.0)</td>
</tr>
<tr>
<td>Upper RTI</td>
<td>51 (13.3)</td>
<td>30 (7.8)</td>
</tr>
<tr>
<td>Viral upper RTI</td>
<td>44 (11.5)</td>
<td>50 (13.1)</td>
</tr>
<tr>
<td>AE leading to d/c*</td>
<td>6 (1.6)</td>
<td>13 (3.4)</td>
</tr>
<tr>
<td>Rash</td>
<td>2 (&lt; 1)</td>
<td>1 (&lt; 1)</td>
</tr>
<tr>
<td>AE of clinical interest</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>36 (9.4)</td>
<td>37 (9.7)</td>
</tr>
<tr>
<td>Neuropsychiatric</td>
<td>60 (15.7)</td>
<td>72 (18.8)</td>
</tr>
</tbody>
</table>

## Available Fixed Dose (FDC) Once Daily NNRTI Combinations

<table>
<thead>
<tr>
<th>FDC</th>
<th>Components</th>
<th>Food</th>
<th>CrCL (cc/min)</th>
<th>Drug Intxn</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atripla™</td>
<td>EFV 600 mg TDF 300 mg/FTC 200 mg</td>
<td>Empty stomach</td>
<td>&gt;50</td>
<td>CYP3A4 Inducer &gt;&gt; inhibitor</td>
</tr>
<tr>
<td>SYMFI Lo™</td>
<td>EFV 400 mg TDF 300 mg/FTC 200 mg</td>
<td>Empty stomach</td>
<td>&gt;50</td>
<td>CYP3A4 Inducer &gt;&gt; inhibitor</td>
</tr>
<tr>
<td>Complera™</td>
<td>RPV 25 mg TDF 300 mg/FTC 200 mg</td>
<td>~ 400 kcal</td>
<td>&gt;50</td>
<td>CYP3A4 substrate PPI C/I</td>
</tr>
<tr>
<td>Odefsey™</td>
<td>RPV 25 mg TAF 25 mg/FTC 200 mg</td>
<td>~ 400 kcal</td>
<td>&gt;30</td>
<td>CYP3A4 substrate PPI C/I</td>
</tr>
<tr>
<td>Delstrigio</td>
<td>DOR 100 mg TDF 300 mg/3TC 300 mg</td>
<td>w/ or w/o food</td>
<td>&gt;50</td>
<td>CYP3A4 substrate</td>
</tr>
</tbody>
</table>

EFV = efavirenz  
RPV = rilpivirine  
TDF = tenofovir disoproxil fumarate  
TAF = tenofovir alafenamide  
FTC = emtricitabine  
3TC = lamivudine
DHHS and IAS ART Guidelines for NNRTI as Initial ART

• When recommended regimens are not available or not an option.
• Avoid if no baseline GT:
  • Transmitted resistance more likely
  • Low genetic barrier
• EFV (and Atripla) no longer recommended
• RPV is smallest FDC with TAF (Odefsey) or TDF (Complera)
  • Lower rate of CNS, rash, lipids vs. EFV
  • Must be taken with food
  • Less effective if baseline VL <100K c/ml and CD4 >200 c/mm3
  • Contraindicated with PPI--requires stomach acid for absorption
  • Active if resistance to EFV, may be similar to etravirine in potency
• DOR: no food or PPI intx; benefit viral resistance; disadvantage TDF
Darunavir/cobi/TAF/FTC (Symtuza)

- First protease inhibitor FDC approved by FDA July 2018
  - Initial ART
    - Switch therapy: HIV VL <50 c/mL on ART for ≥6 mo and no resistance
- Dosage: one tablet daily with food
  - Tablet can be split in 2 pieces and consumed immediately.
- Bioavailability: DRV and cobi ↑ 40-50% with high fat meal
- Avoid if CrCL < 30 cc/ml.
- Avoid in severe liver impairment (C/P C)
- Drug interaction potential
  - DRV/c inhibits CYP3A and CYP2D6
  - Cobicistat inhibits PgP, BCRP, MATE1, OATP1B1 and OATP1B3
Darunavir/cobi/FTC/TAF-Symtuza

• Why select an PI based regimens
  • Pros:
    • FDC with low pill burden
    • High genetic barrier to resistance.
    • Consider if no baseline GT available
    • Lower risk of renal and bone toxicity with TAF component
  • Cons:
    • Negative effects on metabolic profile (liver, lipids, etc)
    • Risk of drug-drug interactions
    • Lower tolerability than other ART
• Comparable virologic efficacy/safety--DRV/c/FTC/TAF vs DRV/c/FTC/TDF (Amber)
• Can change DRV/r or DRV/c based regimen to FDC with continued VL suppression (Emerald)
Darunavir/cobi/FTC/TAF-Symtuza

**AMBER: randomized, double-blind phase III trial**

- Tx-naive pts \( n = 725 \)
- DRV/cobi/FTC/TAF \( n = 362 \)
- DRV/cobi + FTC/TDF \( n = 363 \)

**EMERALD: randomized, open-label phase III trial**

- HIV-1 RNA < 50 c/mL for ≥ 2 mo on boosted PI + FTC/TDF ≥ 6 mo; no previous VF on DRV; eGFR ≥ 50 mL/min \( n = 1141 \)
- Switch to DRV/c/FTC/TAF \( n = 763 \)
- Continue Boosted PI + FTC/TDF \( n = 378 \)

AMBER: Efficacy at Wks 48 and 96

- No difference b/t VL> or <100K, CD4 > or < 200, age, sex, or race
- No evidence of DRV or TDF mutations

**HIV-1 RNA < 50 copies/mL (%)**

<table>
<thead>
<tr>
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<th>Wk 48</th>
<th>Wk 96</th>
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<tr>
<td><strong>DRV/COBI + FTC/TDF</strong> (n = 363)</td>
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</tbody>
</table>

- Diarrhea (9%) rash (6%), n (6%)
- Lower AE d/c’s DRV/c/FTC/TAF vs DRV/c/FTC/TDF (1.9% vs 4.4%)
- Less effects bone, renal markers w/ DRV/c/FTC/TAF
- ↑ eGFR DRV/cI/FTC/TAF \( p = .001 \)
- No Fanconi syndrome
- Similar lipid changes across arms
**EMERALD: Switch From Boosted PI/F/TDF to DRV/c/F/TAF in Suppressed Pts**

- Boosted PI = DRV/r or DRV/c or lopinavir/ritonavir/TDF/FTC (n=363)
- Switched to DRV/c/FTC/TAF (n=763)

**Treatment difference: 1.2%**
(95% CI: -1.7% to 4.1%)

**Treatment difference: 0.4%**
(95% CI: -1.5% to 2.2%)

**VL suppression maintained @96 wks**

- ADRs similar (≥5% in both group)

<table>
<thead>
<tr>
<th></th>
<th>Switch</th>
<th>Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngitis</td>
<td>81 (11%)</td>
<td>39 (10%)</td>
</tr>
<tr>
<td>Upper RTI</td>
<td>81 (11%)</td>
<td>39 (10%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>60 (8%)</td>
<td>16 (4%)</td>
</tr>
<tr>
<td>Headache</td>
<td>58 (8%)</td>
<td>16 (4%)</td>
</tr>
<tr>
<td>Back pain</td>
<td>54 (7%)</td>
<td>21 (6%)</td>
</tr>
<tr>
<td>Vit D deficiency</td>
<td>50 (7%)</td>
<td>27 (7%)</td>
</tr>
<tr>
<td>Osteopenia</td>
<td>38 (5%)</td>
<td>21 (6%)</td>
</tr>
</tbody>
</table>
Similar eGFR by serum creatinine b/t groups (p=.092);

Increased eGFR by cystatin c with DRV/c FDC (p=.034)

Significant improvements in hip/spine BMD for DRV/c FDC vs baseline PI (control)

Improved bone and renal parameters after switch

# Guidelines: Initial PI Based ART Recommended In Certain Clinical Situations

<table>
<thead>
<tr>
<th>Protease Inhibitor (PI)</th>
<th>Two “NUCs”</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Symtuza (DRV 800/cobi150/TAF10/FTC 200 mg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ DRV+ ritonavir 100 mg or 150 mg cobicistat (Prezcoibix)</td>
<td>Tenofovir AF 25mg* plus FTC (Descovy) OR Tenofovir DF /FTC (Truvada) OR Abacavir/lamivudine (Epzicom) **Only if HLAB5701 neg</td>
<td>*IAS recommends F/TAF vs F/TDF -DRV preferred if concern about resistance/ adherence -sulfa moiety; SJ, rash -GI-n/diarrhea; HBV flare --CYP3A4 interactions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ATV not recommended by IAS --ATV less well tolerated vs DRV -lower CV events-less progression of atherosclerosis (carotid artery intima medial thickness) --ADR ↑bili/jaundice, --Avoid renal dysfunction--stones --CYP3A4 interaction</td>
</tr>
<tr>
<td>Atazanavir 300 mg + ritonavir 100 mg OR cobicistat 150 mg (Evotaz)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ One daily w/ food</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DHHS and IAS ART Guidelines 2018

Switching Ritonavir to Cobicistat Boosting and Visa Versa

- **Ritonavir: (/r)**
  - Inhibits CYP3A4, 1A2, 2B6, 2C19,2C8, 2C9, pgp, BCRP, OATPs, MATE1
  - *induces* CYP1A2, 2B6, 2C9, 2C19 and UGT
- **Cobicistat (/cobi)**
  - Inhibits CYP3A, 2D6, pgp, BRCP, OATP1B1, OATP1B3, MATE1
  - No induction

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cobicistat</th>
<th>Ritonavir</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>Potential ↑ MS; No intxn</td>
<td>↓AUC w/ PI/r</td>
<td>Ritonavir induction</td>
</tr>
<tr>
<td>hydromorphone</td>
<td>hydromorphone</td>
<td></td>
<td>Monitor W/D</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>rosu 10 mg + EVG/c ↑statin</td>
<td>rosvas 10</td>
<td>Differences in 3A4 inhibition. Max rosvu</td>
</tr>
<tr>
<td></td>
<td>AUC38%,Cmax 89%, Cmin 43%</td>
<td>mg/d + DRV/r</td>
<td>10-20 mg/day</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>↑AUC 127%; avoid co-</td>
<td>No effect</td>
<td>Cobi inhibition of intestinal pgp transport</td>
</tr>
<tr>
<td></td>
<td>administration or ↓75 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>bid</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Ritonavir and cobi may not provide same interactions
- Requires 1-2 wks for enzyme induction to occur/subside
- Check all interactions when changing b/t cobi and /ritonavir

Ibalizumab (IBA, Trogarzo)

- Monoclonal Ab- derived from mouse, binds CD4 receptor on T-cell, preventing changes in gp120 needed for viral entry
- Effective in both CCR5 and CXCR4 tropic strains
- FDA Approved March 2018
- Dosage: IV LD 2,000 mg followed by a IV 800 mg q 2 wks
  - after dilution in 250 mL of 0.9% NACL
- Phase 3 open label single group study n=40 with MDR HIV
- At week 25, ibalizumab + OBR had mean decrease in VL 1.6 log10 copies/ml from baseline (43% <50; 50% <200)
- 17 (43%) with fostemsavir (investigational attachment inhibitor)
- Diminished ibalizumab susceptibility in vitro in pts with virologic failure

TMB-301: LA IBA in Tx Experienced PLWH Infected With Multidrug-Resistant HIV

- Single-arm, OL phase III (n=40) mean CD4 140c/mm³,
- HIV VL > 1000c/ml on ART ≥ 6 mo,
- Primary endpoint: ≥ 0.5 log₁₀ HIV-1 RNA ↓ @ Day 14

HIV-1 VL resistant to ≥ 1 ARV from 3 classes, sensitive to ≥ 1 ARV for OBR
43% (17) received fostemsavir

83% w/ ↓ 0.5 log VL @ D14 vs 3% on ART (p <.001)
60% w/ ↓ 1 log VL
Mean VL ↓ 1.1 log
18% (n=7) VL failures

80% (n=32) AE’s
- Diarrhea (20%)
- Nausea, fatigue, fever, dizziness
- Rash (13% each)

Serious AEs 23% (n=9),
- IRIS (n=1)
- D/C (n=5, 13%)
No anti-IBA Ab

TMB-311: IBA + OBR in Tx-Experienced Pts With Multidrug Resistance Virus

- TMB-311 evaluated efficacy and safety of IBA + OBR through Wk 48 in tx exp PLHIV w/ MDR @ 24-wk TMB-301 trial (n = 27)
  - CD4+ ↑ @ Wk 24 = Wk 48
  - 24/27 pts (89%) completed Wk 48
  - D/c for consent withdrawal (n = 2), AE unrelated to treatment (n = 1)
  - No anti-IBA antibodies detected

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TMB-311 (n = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, yrs</td>
<td>53</td>
</tr>
<tr>
<td>Median HIV-1 RNA, log₁₀ c/mL</td>
<td>4.3</td>
</tr>
<tr>
<td>Median CD4+ cells/mm³</td>
<td>102</td>
</tr>
<tr>
<td>Virus resistance, n (%)</td>
<td></td>
</tr>
<tr>
<td>- Exhausted ≥ 3 ARV classes</td>
<td>16 (59)</td>
</tr>
<tr>
<td>- Exhausted ≥ 4 ARV classes</td>
<td>9 (33)</td>
</tr>
<tr>
<td>- Resistant to all approved ARVs</td>
<td>4 (15)</td>
</tr>
</tbody>
</table>

# TMB-311: Efficacy and Safety Outcomes With IBA Thru Wk 48 Expanded Access

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Ibalizumab + OBR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median HIV-1 RNA reduction, log(_{10}) c/mL</td>
<td></td>
</tr>
<tr>
<td>Wk 24</td>
<td>2.5</td>
</tr>
<tr>
<td>Wk 36</td>
<td>2.8</td>
</tr>
<tr>
<td>Wk 48</td>
<td>2.8</td>
</tr>
<tr>
<td>Wk 24 viral suppression rate, % (N = 40)</td>
<td></td>
</tr>
<tr>
<td>HIV-1 RNA &lt; 50 c/mL</td>
<td>43</td>
</tr>
<tr>
<td>HIV-1 RNA &lt; 200 c/mL</td>
<td>50</td>
</tr>
<tr>
<td>Wk 48 viral suppression rate, % (n = 27)</td>
<td></td>
</tr>
<tr>
<td>HIV-1 RNA &lt; 50 c/mL</td>
<td>59</td>
</tr>
<tr>
<td>HIV-1 RNA &lt; 200 c/mL</td>
<td>63</td>
</tr>
<tr>
<td>Mean CD4+ cell count increase from BL to Wk 24, cells/mm(^3)</td>
<td>62</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment-Emergent MILD/MODERATE AE %</th>
<th>TMB-311 Pts (n = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infection</td>
<td>15</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>11</td>
</tr>
<tr>
<td>Rash</td>
<td>7</td>
</tr>
</tbody>
</table>

Which is recommended in treatment naïve HIV infected persons per ARV Guidelines?

A. ABC/3TC/dolutegravir (Triumeq)
B. TAF/FTC/bictegravir (Biktarvy)
C. TAF/FTC/Elvitegravir/cobi (Genvoya)
D. TAF/FTC/darunavir/cobi (Symtuza)
E. TDF/3TC/Doravirine (Delstrigo)
F. TAF/FTC/Ibalizumab (Trogarzo)

PMH: DM, HTN, CHF s/p MI
Meds: amlodipine, furosemide, carvedilol, losartan, metformin
Labs:  CD4 544 c/mm3  HIV VL 69,000 c/ml  A1C 7.1%
       AST/ALT/BUN/Scr WNL  HbsAG neg, HBsAB reactive  LDL 100 mg/dl/HDL 60
       HIV Genotype and HLA B5701 pending
Why Are INSTI Based ART Preferred for Initial ART?

• Efficacy comparable to boosted PI regimens
• Single FDC formulations available
• High genetic barrier to resistance (e.g. dolutegravir, bictegravir) vs RAL and EVG/c
• Lowest potential for drug interactions
• ADRs: Well tolerated
  • Pros: Neutral impact on CV, metabolic, lipids
  • Cons: ?? weight gain
Dolutegravir (Tivicay)

- FDC with ABC/3TC (Triumeq) only if HLA B5701 neg
- VL suppression was similar/superior to 1st gen INSTI, NNRTI and PI
- Recommended as initial ART therapy if HLA neg
- Higher genetic barrier than RAL or EVG; rare baseline resistance
- Given once daily with/without food
  - Food: ↑41% with moderate fat, ↑66% levels with high fat meal
- Lower DTG AUC if CrCL < 30 cc/min; not cleared by dialysis
- Inhibits OCT2 → ↓ tubular secretion Scr; mean ↑ Scr 0.1-0.3 mg/dL (4 wks)
- Well tolerated; neuropsychiatric sx (similar to efavirenz), WT gain?
- Fewer drug interactions since no CYP450 enzymes

Tivicay and Triumeq package insert
Neuropsychiatric-Associated Dolutegravir Discontinuation in German Cohort (N=1704)

- Retrospective (2007 to 2016)
- 6% D/C DTG 6-12 mo (range 3 to 6%)
- Onset 3.1 mo
  - Risk factors: Females HR (2.64),
  - Age > 60yr (HR 2.86), ABC (HR 2.42)
  - Reversible D/C (n=6/6 re-challenge

<table>
<thead>
<tr>
<th>D/C Reason</th>
<th>DTG (n = 985)</th>
<th>EVG/c (n = 287)</th>
<th>RAL (n = 678)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE, n (%)</td>
<td>67 (7.6)</td>
<td>27 (7.6)</td>
<td>28 (3.3)</td>
</tr>
<tr>
<td>Neuropsychiatric AE, * n (%)</td>
<td>49 (5.0)</td>
<td>36 (3.7)</td>
<td>14 (1.9)</td>
</tr>
<tr>
<td>Sleep disturbances</td>
<td>36 (3.7)</td>
<td>2 (0.7)</td>
<td>4 (0.6)</td>
</tr>
<tr>
<td>▪ Poor concentration</td>
<td>8 (0.8)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>▪ Dizziness</td>
<td>13 (1.3)</td>
<td>1 (0.3)</td>
<td>3 (0.4)</td>
</tr>
<tr>
<td>▪ HA/paresthesia</td>
<td>16 (1.6)</td>
<td>1 (0.3)</td>
<td>6 (0.9)</td>
</tr>
<tr>
<td>▪ Depression</td>
<td>7 (0.7)</td>
<td>0 (0)</td>
<td>1 (0.1)</td>
</tr>
</tbody>
</table>

### Selected Dolutegravir Drug Interactions

<table>
<thead>
<tr>
<th>Medication</th>
<th>Interaction</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyvalent cations (e.g., Mg, Al, Fe, or Ca)</td>
<td>Concurrent Al+ Mg+ antacids ↓ DTG AUC 76% vs 26% if staggered.</td>
<td>Administer Al++, Mg++, or Ca+-antacids, laxatives, iron, sulcrafate 6 hrs before or 2 hrs after DTG</td>
</tr>
<tr>
<td>Antacids, laxatives, sulcrafate, buffered meds</td>
<td>Fasting: DTG AUC↓ 37%-39% w/CA+; ↓54%-57% with iron Food: normal AUC</td>
<td>Take DTG and calcium or iron together with food.</td>
</tr>
<tr>
<td>Rifampin</td>
<td>↓ DTG</td>
<td>↑ DTG 50 mg BID if INSTI-naïve. Consider rifabutin.</td>
</tr>
<tr>
<td>Metformin</td>
<td>Daily DTG ↑ Metformin AUC 79%, Cmax 66%, Cmin 9%; BID DTG ↑metformin AUC 2.4 fold, Cmax 2 fold, Cmin 14%</td>
<td>Adjust metformin to 1000 mg max daily. Adjust metformin if stopping/starting DTG</td>
</tr>
</tbody>
</table>

DHHS HIV Guidelines 2018; J Antimicrob Chemother 2017;72: 1842
## Selected DTG Drug Interactions

<table>
<thead>
<tr>
<th>Medication</th>
<th>Interaction</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multivitamins</td>
<td>DTG AUC (\downarrow) 33%</td>
<td>Standard DTG dosage</td>
</tr>
<tr>
<td>PPI and H2 blockers</td>
<td>No interaction</td>
<td>Standard DTG dosage</td>
</tr>
<tr>
<td>HCV DAAs</td>
<td>No interactions</td>
<td>Standard DTG dosage</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>No interactions</td>
<td>Standard DTG dosage</td>
</tr>
<tr>
<td>Losartan, amlodipine, furosemide, carvedilol</td>
<td>No interactions</td>
<td>Standard DTG dosage</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>(\downarrow) DTG</td>
<td>Avoid, DTG bid with carbamazepine, consider oxacarbamazepine</td>
</tr>
<tr>
<td>Dofelitide</td>
<td>(\uparrow) dofelitide</td>
<td>Avoid co-administration</td>
</tr>
</tbody>
</table>

DHHS HIV Guidelines 2018; Liverpool HCV drug interaction
Bictegravir 50 mg/TAF25mg/FTC 200 mg (Biktarvy)

• FDA approval 2/2018 Smallest FDC INSTI
  • Initial ART for treatment naïve
  • Switch if VL UD 3 mo; no VL failures or resistance
• Recommended by both ART guidelines as initial ARV therapy
• High barrier to resistance, including some DTG resistant strains
• High virologic efficacy and good tolerability up to 48 wks
• One tablet daily w/without food (t1/2 = 16 to 20 hr)
• Avoid if CrCl < 30 cc/ml
• Baseline Scr, PO4 , est CrCl, urine glucose, protein, PO4
• Hepatic metabolism: CYP3A4 and UGT1A1 substrate
• Low potential for DI but affected by 3A4 inducers/inhibitors

https://aidsinfo.nih.gov/drugs/570/bictegravir/0/professional
BIC/FTC/TAF vs DTG/ABC/3TC in Treatment-Naive Adults (n=629)

- MC, R, DB, phase III trial
- TN adults HIV VL > 500c/ml, eGFR > 50 ml/min
- Primary outcome: HIV VL < 50 copies/mL @ Wk 48

### VL response @48 wks

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>VL &lt;50c/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>BIC/FTC/TAF daily+ DTG/ABC/3TC Placebo daily (n = 314)</td>
<td>92.3</td>
</tr>
<tr>
<td>DTG/ABC/3TC daily + BIC/FTC/TAF Placebo daily (n = 315)</td>
<td>93</td>
</tr>
</tbody>
</table>

- BIC vs DTG 87.9% vs 89.8% VL <50c/ml maintained @ 96 wks
  - Nausea less w/ BIC/FTC/TAF (n=6, 10%) vs DTG/ABC/3TC (n=17, 23%) (p< .0001)
  - BM changes similar in both arm
  - No cases of renal or proximal tubulopathy in TAF arm
  - Greater ↑ total/LDL cholesterol with BIC/TAF/FTC vs DTG/ABC/3TC arm

**BIC/F/TAF vs DTG+F/TAF in Treatment-Naive Adults (n=645)**

- MC, R, DB, phase III trial stratified by HIV VL and CD4
- TN adults HIV VL > 500c/ml, eGFR > 30 ml/min
- Primary outcome: HIV VL < 50 copies/mL @ Wk 48

**VL response @48 wks**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BIC/FTC/TAF daily + DTG/FTC/3TC Placebo daily</td>
<td>89%</td>
</tr>
<tr>
<td>DTG+ FTC/TAF daily + BIC/FTC/TAF Placebo daily</td>
<td>93%</td>
</tr>
</tbody>
</table>

- BIC vs DTG 84% vs 86% VL <50c/ml maintained @ 96 wks
- Fewer treatment-related AEs w/ BIC/F/TAF vs DTG + F/TAF (p = .02)
- Nausea, diarrhea, headache similar in both arms
- Grade 3/4 laboratory abnormalities similar between arms
- No tubulopathy, d/c for renal ADRs, or differences in lipids in either arm

## Bictegravir Selected Drug Interactions

<table>
<thead>
<tr>
<th>BIC inhibits OCT2 and MATE1</th>
<th>dofetilide C/I (↑ OCT2/MATE1 substrates)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BIC is UGT1A1 and CYP3A4 substrate</td>
<td>Strong 3A4 and UGT1A1 inducers/inhibitors can alter BIC levels</td>
</tr>
<tr>
<td>UGT1A1 <em>and</em> CYP3A4 inhibitor</td>
<td>BIC ↑ 315% by atazanavir (dual inhibitor): C/I</td>
</tr>
<tr>
<td>CPY3A4 Inhibitor</td>
<td>↑ BIC 61-74% w/ 3A4 inhibitors DRV/c, voriconazole</td>
</tr>
</tbody>
</table>

### Bictegravir Selected Drug Interactions

<table>
<thead>
<tr>
<th>Interactions</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UGT1A1 and CYP3A4 Inducer</strong></td>
<td>Rifabutin is weak dual inducer (BIC exposure ↓ 38%). Avoid co-administration</td>
</tr>
<tr>
<td><strong>CYP3A4, UGT1A1, P-gp inducers: rifampin, anticonvulsant, St.John’s wort</strong></td>
<td>↓ BIC AUC 75%. Avoid co-administration.</td>
</tr>
<tr>
<td><strong>Al-Mg, CA containing (antacids, sucrafate), iron</strong></td>
<td>Dose BIC ≥ 2 hrs <strong>before</strong> antacids (↓ 13% vs 52% after antacids). Dose BIC/Fe/CA w/ food.</td>
</tr>
<tr>
<td><strong>Metformin</strong></td>
<td>Metformin ↑ 39%; no dose adjustments except if renal insufficiency</td>
</tr>
<tr>
<td><strong>Amlodipine, furosemide, carvedilol, losartan</strong></td>
<td>No interactions, standard BIC dose</td>
</tr>
</tbody>
</table>

**Raltegravir HD (Isentress HD) 600 mg Film Tablets**

- Must be swallowed whole with or without food
- Metabolism via a UGT1A1-mediated glucuronidation pathway
- No adjustments in renal insufficiency
- SE: insomnia, HA, dizziness, nausea, fatigue, fatal skin rx, myositis

<table>
<thead>
<tr>
<th>Patients</th>
<th>Dosage</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naïve or HCV VL Suppressed on RAL 400 mg bid; Pediatric WT &gt;40kg</td>
<td>1200 mg (600 mg X 2) daily with or without food</td>
<td>Not interchangeable with chewable or oral suspension</td>
</tr>
<tr>
<td>Treatment experienced</td>
<td>400 mg BID</td>
<td>HD dosing not available</td>
</tr>
<tr>
<td>Co-administered with rifampin</td>
<td>2X 400 mg BID</td>
<td>HD dosing not available</td>
</tr>
</tbody>
</table>

Wk 48 HIV-1 RNA < 40 copies/mL in pts with BL HIV-1 RNA > 100,000 copies/mL:
RAL Daily, 86.7%; RAL BID, 83.8% (Δ 2.9; 95% CI: -6.5-14.1)
RAL daily associated with overall safety profile similar to RAL BID

## Selected Raltegravir Drug Interactions

<table>
<thead>
<tr>
<th>Medication</th>
<th>Interaction</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| Al-Mg containing antacids        | RAL Cmin ↓ 49% - 63% | Avoid with RAL 400 mg tabs  
Consider Ca-containing antacids  
NaHCO3 ↑ RAL absorption          |
| CA- containing antacids          | RAL HD Cmin ↓ 48%-57%| Avoid with RAL HD 1200 mg daily.                    |
| Rifampin                         | ↓ RAL                | Give RAL 800 mg bid.  
Avoid with RAL HD 1200 mg tabs   |
| Anticonvulsants                  | ↓ RAL                | Co-administration not recommended                   |
| Losartan, amlodipine, carvedilol | No interaction       | Standard RAL dosing                                 |
| furosemide                       |                      |                                                     |

RAL package insert, Liverpool HIV drug interaction website, Reynolds H et al. CROI 2018, Abst 470
### DHHS Guidelines: Initial INSTI Based Regimens Recommended for Most PLWH

<table>
<thead>
<tr>
<th>INSTI</th>
<th>PLUS 2 Nucleosides NRTIs)</th>
<th>Dosage (w/o food)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bictegravir 50 mg</td>
<td>TAF 25 mg/FTC 200 mg</td>
<td>One FDC daily (Biktarvy™)</td>
</tr>
<tr>
<td>Dolutegravir 50 mg</td>
<td>ABC 600 mg/3TC 300 mg if HLA B5701 neg</td>
<td>One FDC tablet daily (Triumeq™)</td>
</tr>
<tr>
<td>Dolutegravir 50 mg</td>
<td>TAF 25 mg/FTC 200 mg (Descovy™) OR TDF 300 mg/F 200 mg (Truvada™)</td>
<td>Two tabs daily</td>
</tr>
<tr>
<td>Raltegravir HD 1200 mg daily (2 X 600 mg tabs) OR RAL 400mg bid</td>
<td>TDF 300 mg/FTC 200 mg (Truvada™) OR TAF 25 mg/FTC 200 mg (Descovy™)</td>
<td>Three tablets daily</td>
</tr>
</tbody>
</table>

### IAS HIV INSTI Guidelines

<table>
<thead>
<tr>
<th>INSTI</th>
<th>PLUS 2 Nucleoside Reverse Transcriptase Inhibitors (NRTIs)</th>
<th>Dosage (w/o food)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bictegravir 50 mg</td>
<td>TAF 25 mg/FTC 200 mg</td>
<td>One FDC daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Biktarvy™)</td>
</tr>
<tr>
<td>Dolutegravir 50 mg</td>
<td>ABC 600 mg/3TC 300 mg if HLA B5701 neg</td>
<td>One FDC tablet daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Triumeq™)</td>
</tr>
<tr>
<td>Dolutegravir 50 mg</td>
<td>TAF 25 mg/FTC 200 mg (Descovy™) OR TDF 300 mg/FTC 200 mg (Truvada™)</td>
<td>Two tabs daily</td>
</tr>
</tbody>
</table>

- TAF recommended instead of TDF
- Raltegravir not recommended –lower barrier to resistance
- Both DHHS and IAS removed EVG/cobicistat as initial INSTI

Why NOT Elvitegravir/cobi 150mg as Initial INSTI?

• PROS
  • Single FDC available
    • TAF 10 mg/FTC 200 mg (Genvoya) CrCL > 30cc/ml
    • TDF 300 mg/FTC 200 mg (Stribild) CrCL > 50cc/ml
  • New labeling (12/2018) in hemodialysis. Administer TAF/FTC/EVG/cobi once daily. On days of HD, administer after HD.

• CONS
  • Lower genetic barrier
  • Must be taken with food
  • AE: diarrhea
  • ↑ risk of 3A4 drug interactions from cobicistat
    • ↑drospirenone w/ hyperK+
    • Start w/ lowest dose of atorvastatin; monitor safety

Genvoya label: drugs@fda Eron JJ et al. Lancet HIV 2019; 6: e15–24
Which is recommended in treatment naïve HIV infected persons per ARV Guidelines?

A. ABC/3TC/dolutegravir (Triumeq)
B. TAF/FTC/bictegravir (Biktarvy)
C. TAF/FTC/Elvitegravir/cobi (Genvoya)
D. TAF/FTC/darunavir/cobi (Symtuza)
E. TDF/3TC/Doravirine (Delstrigo)
F. TAF/FTC/Ibalizumab (Trogarzo)

PMH: DM, HTN, CHF s/p MI
Meds: amlodipine, furosemide, carvedilol, losartan, metformin
Labs: CD4 544 c/mm³ HIV VL 69,000 c/ml A1C 7.1%
       AST/ALT/BUN/Scr WNL HbsAG neg, HBsAB reactive LDL 100 mg/dl/HDL 60
       HIV Genotype and HLA B5701 pending
Weight Gain, An ADR of INSTIs?

- Studies suggest an association of INSTI with wt gain/obesity
- Switch studies: 1.3 to 2.9 kg, +5.3 kg DTG from EFV, no diff b/t INSTI
- Greatest risk for ↑ WT: AA, women, age >60 yrs
- Not measured prospectively in phase III trials of INSTI—white males
- Unclear if these changes are statistically significant but seem greater than compared to other ART classes (e.g. NNRTI or PI)
- Ongoing studies in Sub-Saharan Africa—more women and AA
- Hypothesis: DTG inhibit the binding of radolabelled α-melanocyte stimulating hormone (MSH) to human recombinant melanocrotin 4 (MC4R) receptor by 64%. MC4R is involved in regulation of food intake and deficiency of MC4R is associated with obesity
### WT Gain in INSTI Switch Studies

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Dates</th>
<th>Outcome</th>
<th>Comments</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTG A5001, A5322 n=972 (81%♂, 50% nonwhite, 50 yrs age, BMI 26.4 kg/m2)</td>
<td>1997-2017 F/U 7.8yr</td>
<td>WT Δ 2 yr pre/post INSTI ♀+1.3 kg vs ♂0.1 kg AA+0.9 kg vs white 0.01kg, Age &gt;60 1.2Kg vs -1.4kg (&lt;40 yr)</td>
<td>Highest risk: ♀, AA, age &gt;60 yrs. ↑wt gain greater than expected for age.</td>
<td>J. Lake et al. CROI 2019, Abstr 669</td>
</tr>
<tr>
<td>WIHS ♀ n=1118 (882 Δ to INSTI vs. 234 no Δ) AA 61%, 48.8yr,</td>
<td>2008-2017 F/U 2 yr</td>
<td>Wt Δ 6-12 mo before/after INSTI Δ +2.14kg, + BMI 0.78kg/mm2, +135% body fat, ↑SBP/DBP 2.24/1.17</td>
<td>significant ↑BW body fat, BP vs. continue on non-INSTI</td>
<td>Kerchberger AM et al. CROI 2019 Abst 672</td>
</tr>
<tr>
<td>N=495 Δ EFV to INSTI or PI or cont EFV</td>
<td>INSTI @ 18 mo</td>
<td>Wt Δ +2.9 kg @18mo (p&lt;0.05) vs EFV 0.9 kg vs PI 0.7kg</td>
<td>DTG +5.3Kg (p,0.05);RAL/EVG/c +2.8 kg (p=0.19)</td>
<td>Norwood J et al. J AIDS 2017 76: 527</td>
</tr>
</tbody>
</table>
## WT Gain When Starting INSTI ART

<table>
<thead>
<tr>
<th>Study Demographics</th>
<th>Dates</th>
<th>Outcome</th>
<th>Comments</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazil, n=1567</td>
<td>2000-2015;</td>
<td>18.3% obese; 37.4/1000 p-years. 10 fold ↑ incidence vs other ART, MV analysis, INSTI (adjust HR 7.12, P&lt;0.0001); other factors: younger age, ♂, ↑ BMI, HIV VL, HTN. DM↓CD4,</td>
<td>Highest risk: ♂, ↑ BMI, HIV VL, HTN. DM↓CD4,</td>
<td>Bakar DR et al. J Antimic Chemother 2018; 73: 2177</td>
</tr>
<tr>
<td>N=21,886,NA-ACCORD, 87% ♂, 43% white, 42 yr, BMI 25 kg/m2. INSTI (n=4112)PI, NNRTI</td>
<td>1/20072 /2015.</td>
<td>Wt Δ INSTI @ 1-2yrs INSTI Δ +4.4, 5.8 kg vs. NNRTI +3.3, 4.1 kg (p&lt;.05) PI +4.3 kg, 5kg PI (p=0.68) +5.6kg DTG, + 5.4kg RAL, +3.4kg (EVG) (p&lt;0.03 vs RAL).</td>
<td>INSTI (i.e. DTG, RAL) ↑ WT gain vs. older NNRTI-class</td>
<td>Boorgik K et al CROI 2019 Abst 670</td>
</tr>
<tr>
<td>n=4048; AA 53.2%, ♂ 29.4%, av age 46.4 yr, baseline BMI 27</td>
<td>2009-2017 (6.7yr f/u)</td>
<td>BMI Δ ♂ 0.25 vs 0.43 ♂ (p=0.001) INSTI 0.39 (AA), 0.32 (Hispanics), 0.15 (White) (p&lt;0.05).</td>
<td>↑AA/Hispanic♂ &gt;♂ PI INSTI; BMI↑ 51% to 65% @ 3yr (p&lt;0.5)</td>
<td>Bedimo R et al. ID week,2018, Abst538</td>
</tr>
</tbody>
</table>
Effects of INSTIs on Body Weight (BW) in Randomized Trials

- **Raltegravir**
  - Trunk fat 7.3% ↑DRV/r/RAL vs. TDF/FTC/RAL @ wk 96 (p=0.021)
  - ACTG 5257 (n=1809)
    - Higher risk of wt gain RAL vs ATV/r or DRV/r/TDF/FTC
    - AA 55% more likely wt gain/obese vs white

- **Dolutegravir**
  - vs PI/r: +1 kg increase BW to wk 48 (p=0.002)
  - vs EFV: BW increases higher in DTG
  - Gilead 1490 (n=631) 57% white, 91% ♂: DTG+3.9 kg, +3.5 kg BIC wk 96
  - DTG monotherapy +4.1 kg @ wk 24

Hill A et al. J. Virus Erad 2019 Jan;5:41
Are Two ARVs Just as Good as Three for Initial ART Therapy?

• Rationale: To avoid NRTI toxicity d/t mitochondria toxicity (eg. hepatic injury, renal damage, pancreatic toxicity, myocardial dysfunction, peripheral and central nervous system impairment)

• ARV Guidelines: regimens with < 2 NRTIs should only be used in PLWH who cannot receive ABC, TAF, or TDF.

• Not yet SOC

• 2 ARV regimens
  • DRV/r + 3TC (ANDES)
  • DRV/r + RAL: only if HIV VL <100K and CD4>200 c/mm3; 17% higher risk of VL failure vs 3 ARVs
  • DTG + 3TC (GEMINI 1,2): pending FDA approval, submitted 10/2018

GEMINI-1 and -2: DTG + 3TC vs DTG + TDF/FTC in Treatment-Naive Patients

- MC, R, DB, phase III noninferiority studies (n=1441); 85% men, 70% white
- VL <500,000 c/ml (20% VL > 100,000 c/mL, no drug resistance, CD4 <200 (n=118, 8%)
- Primary endpoint: HIV-1 VL < 50 c/mL at Wk 48
- Ongoing with 96 and 144 wks to be reported

VL <50 =91.5% vs 93%
-1.7%, 95% CI -4.4 to 1.1%

GEMINI-1 and -2: VL Response by CD4 Count and Safety @ 48Wks

<table>
<thead>
<tr>
<th>Baseline CD4+ Cell Count, cells/mm³</th>
<th>Patients With HIV-1 RNA &lt; 50 c/mL (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>526/564 531/564 129/140 138/153 605/653 618/662 50/63 51/55</td>
</tr>
</tbody>
</table>

### Safety Event, n (%)

<table>
<thead>
<tr>
<th>Safety Event</th>
<th>DTG + 3TC (n = 716)</th>
<th>DTG + TDF/FTC (n = 717)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>543 (76)</td>
<td>579 (81)</td>
</tr>
<tr>
<td>AE in ≥ 5% of patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Headache</td>
<td>71 (10)</td>
<td>75 (10)</td>
</tr>
<tr>
<td>- Diarrhea</td>
<td>68 (9)</td>
<td>77 (11)</td>
</tr>
<tr>
<td>- Nasopharyngitis</td>
<td>55 (8)</td>
<td>78 (11)</td>
</tr>
<tr>
<td>- Upper RTI</td>
<td>56 (8)</td>
<td>44 (6)</td>
</tr>
<tr>
<td>- Nausea</td>
<td>27 (4)</td>
<td>53 (7)</td>
</tr>
<tr>
<td>- Insomnia</td>
<td>27 (4)</td>
<td>45 (6)</td>
</tr>
<tr>
<td>- Pharyngitis</td>
<td>36 (5)</td>
<td>32 (4)</td>
</tr>
<tr>
<td>- Back pain</td>
<td>35 (5)</td>
<td>31 (4)</td>
</tr>
<tr>
<td>Drug-related AE</td>
<td>126 (18)</td>
<td>169 (24)</td>
</tr>
<tr>
<td>AE leading to withdrawal</td>
<td>15 (2)</td>
<td>16 (2)</td>
</tr>
<tr>
<td>- Neuropsychiatric</td>
<td>6 (&lt;1)</td>
<td>4 (&lt;1)</td>
</tr>
<tr>
<td>Any serious AE</td>
<td>50 (7)</td>
<td>55 (8)</td>
</tr>
</tbody>
</table>
Case Presentation

MP is a 28 year old HIV+ female who is picking up a refill for dolutegravir/3TC/ABC (Triumeq) one tablet daily. She is on her 2nd month of Triumeq and her VL is UD. She is otherwise healthy and has no other medical issues. She mentions that she is trying to get pregnant while her husband is starting PrEP.

What recommendations do you have at this time? How should MP be counseled?

- A) Counsel her husband to stop PrEP to prevent teratogenicity
- B) Counsel to prevent pregnancy to avoid an HIV infected baby
- C) Refuse to dispense Triumeq and call MD to change ART
- D) Educate about risk of teratogenicity w/ Triumeq and inform MD
What is Pre-exposure (PrEP)

- TDF/FTC prophylaxis for an HIV-uninfected person **before** potential exposure to HIV thru sexual or IDU (HIVprevention)
- 2012 FDA approval; adolescents 77lb+(2018)
- Highly protective, not 100%
- To optimize protection/↓STDs, condoms can be helpful
- 6 failures despite adherence
- 100,000 users of PrEP in 2017
- Key to halting HIV transmissions

### Table: PrEP Efficacy

<table>
<thead>
<tr>
<th>Trial</th>
<th>Subjects</th>
<th>N</th>
<th>Drug</th>
<th>HIV Incidence /100 py</th>
<th>HIV Efficacy</th>
<th>ADRs</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROUD</td>
<td>MSM</td>
<td>544</td>
<td>TDF/FTC</td>
<td>4.9</td>
<td>86%</td>
<td></td>
</tr>
<tr>
<td>IPERGAY</td>
<td>MSM</td>
<td>400</td>
<td>TDF/FTC on demand</td>
<td>0.91</td>
<td>86%</td>
<td>GI: 14% vs 5% PBO (p=0.002) Renal: 18% vs PBO 10% (p=0.03)</td>
</tr>
<tr>
<td>US PrEP Demo</td>
<td>MSM, Transgender</td>
<td>437</td>
<td>TDF/FTC</td>
<td>0.43</td>
<td>80-85%</td>
<td></td>
</tr>
<tr>
<td>Kaiser</td>
<td>MSM</td>
<td>753</td>
<td>TDF/FTC</td>
<td>0</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Kaiser NC</td>
<td>MSM, females</td>
<td>972</td>
<td>TDF/FTC</td>
<td>0 (2 d/c PrEP)</td>
<td>100%</td>
<td>15% GFR &lt;70 cc/min 5 d/c due to ↓GFR</td>
</tr>
</tbody>
</table>

Discover: Phase 3, R, MC, DB
\(n=2694\) TAF; 2693 TDF

- 94 sites, 11 countries
- Cis men, TGW@high sexual HIV
- 2+ condomless anal sex 12 wks or STDs 24 wk
- F/u 2 years
- Well tolerated, better bone/renal safety
- TAF effective/safer vs TDF

Hare B et al. CROI 2019, Seattle, WA, Abst 104LB
Daily F/TAF vs F/TDF for PrEP

Renal Safety Through Week 48
Secondary Endpoint

- Renal discontinuations: F/TAF, n=2; F/TDF, n=6
- Fanconi syndrome: F/TAF, n=0; F/TDF, n=1

Bone Safety at Week 48: Bone Mineral Density Sub-study (n=383)
Secondary Endpoint

Hare B et al. CROI 2019, Seattle, WA, Abst 104LB


- 77,120 PrEP users; ≈50% located 5 states: NY, CA, FL, TX, IL
- Southern US: accounted for 52% of new HIV dx, but 30% of PrEP users; limited access; 30 min drive to nearest clinic
- Persistence 2/5 users in 2nd yr; ↑ d/c in 18-24yr old
- Cost prohibitive
- Pharmacists can reduce barriers by ↑ adherence support and expanding PrEP access

Pharmacist Roles: HIV Prevention/PrEP

- Ensure neg HIV Ag/Ab, HBsAg, pregnancy before starting
- Offer HBV vaccination if appropriate
- Familiar w/use/interpretation of HIV test
- Knowledge about HIV and its transmission
- Acquisition of PrEP: authentic sources, funding
- Medication adherence counseling and education (e.g. text messaging reminders)

- Safe sex/condom use/risk reduction
- PrEP does not protect against STI
- Minimize F/TDF ADR’s
- Reminders: regular HIV/preg/renal monitoring
- Avoid nephrotoxins; ↑ hydration
- Recognition signs/sx acute HIV
- Long term toxicity or fetal exposure unknown
- Linkage/referral for HIV care
A Pharmacist-run HIV PrEP Clinic In A Community Pharmacy

- Pharmacist-managed PrEP clinic (Kelley-Ross Pharmacy) in Seattle, WA
- One-Step PrEP™ created March 2015 under MD oversight with a collaborative drug therapy agreement (CDTA) allows access to PrEP.
- Pharmacists take medical/sexual history, perform risk assessment, lab testing, provide patient education, and prescribe/dispense F/TDF.
- Results: 3/2015--3/2016: n=373 sought PrEP; 245 (98%) initiated PrEP, and 210 (84%) identified as MSM
- 1 HIV seroconversion; 75% retention rate
- Higher-than-expected response from MSM seeking PrEP in a community pharmacy setting
- Financially feasible

Tung E et al. Sexual Health, 2018, 15, 556; 23rd CROI 2017, SF, CA Abst 961
How Long Before the HIV Negative Partners Can Stop PrEP?

- Partners Demonstration Project: PrEP as a Bridge to ART
- OL Prospective Study
- Kenya and Uganda (n=1013)
- Heterosexual discordant couples not on ART or PrEP
- PrEP X 6 mo in HIV neg partner then stopped
- HIV+ partner started ART,
- Results: HIV 0.2 vs expected 5.2/100 py (p<0.001)
- Consistent UD VL 6 mo or more

Please PrEP Me: Directory

Search for providers in your area. In collaboration with PrEPLocator.org.

Please PrEP Me: Connect

Helping Californians find PrEP/PEP services in their area through chat, text and telephone, in English and Spanish.

In collaboration with Project Inform and the Office of AIDS, California Department of Public Health.

Please PrEP Me: Resources

Local HIV-prevention resources in English and Spanish for patients and providers in all 50 states.

Please PrEP Me: Global

A worldwide directory of PrEP providers.
Case Discussion

• You dispense a new prescription written for tenofovir disoproxil fumarate/emtrictabine (Truvada) one tablet daily prn PrEP. The 28 yr old cis gender female states that her provider told her she just needs to take the medication before sex with her HIV infected husband.

• How would you counsel her? What would you inform the prescriber?
IPERGAY: On-Demand PrEP (2:1:1)

Dosing Schedule

2 tabs (TDF/FTC) w/food 2-24 hrs before sex

- Sexual Event
- 1 tab (TDF/FTC) 24 hrs later
- 1 tab (TDF/FTC) 48 hours later

Monday Tuesday Wednesday Thursday Friday Saturday Sunday

Total tablets = 4 tablets for HIV prophylaxis

• Multiple exposures: one tablet/day until last exposure, then 2 tablets
• If< 1 week between exposures, LD=1 tablet only
• Effective in MSM only, no data in women or IDU

TDF/FTC for On-Demand PrEP

- Off-label in the US – not recommended by US PrEP guidelines
- IAS guidelines recommend MSM only; optimal if taken 24 hr before sex
  - Data/studies in MSM suggest that 3-4 days/wk (average) effective.
  - Requires careful consideration, patient discussion, frequency of sex acts, ability to plan ahead for medication use
- Not recommended for cis-gender or transgender females
  - TDF conc 10-100 fold higher rectal vs vaginal in cis-gender females
  - TDF cleared more rapidly from vaginal than rectal tissues
  - Lower TDF conc in cis gender females using estrogens
  - PK suggests women need to take daily TDF/FTC 6-7 days/wk
  - Avoid intermittent or ON-demand PrEP in females or in IDU.

Selected ART Updates in Pregnancy

- Treat pregnant = nonpregnant person—consider maternal and fetal HIV risks and teratogenicity
- INSTI
  - Dolutegravir
  - Elvitegravir/cobicistat
  - Raltegravir
- Cobicistat and ritonavir boosted protease inhibitors
  - Darunavir
  - Atazanavir
- NNRTI: Efavirenz, rilprivine, doravirine
- NRTIs: Tenofovir DF and tenofovir AF
Dolutegravir and Neural Tube Defects (NTD)

Deliveries up to 5/2018

- **ARV started at conception**
  - **DTG**: 0.94% (n=4/426) (95%CI 0.37%, 2.4%)
  - **Non-DTG ART**: 0.12% (n=14/11,300) (95%CI 0.07%, 0.21%)
  - **EFV**: 0.05% (n=3/5,787) (95%CI 0.02%, 0.15%)

- **ARVs started during pregnancy**:
  - **DTG**: 0.0% (n=0/2,812) (95%CI 0.0%, 0.13%)
  - **Non-DTG ART**: 0.05% (n=3/5,624) (95%CI 0.02%, 0.16%)
  - **HIV-uninfected**: 0.09% (n=61/66,057) (95%CI 0.07%, 0.12%)

Elvitegravir/cobicistat

- IMPAACT 1026; intensive pK, n=30
- Pregnancy vs. postpartum
- COBI AUC ↓ 44% in 2nd trimester; ↓ 59% in 3rd trimester
- EVG AUC ↓ 24% in 2nd trimester; ↓ 44% in 3rd trimester
- About 80% in 2nd trimester and 70% in 3 trimester had trough concentrations below the EC95* for EVG.
- Avoid COBI (EVG/cobi) among women starting in 2nd trimester
  - Avoid EVG/cobi (e.g. Stribild, Genvoya)
  - What about cobicistat boosted darunavir and atazanavir

- EC95: concentration needed to inhibit 95% of viral replication
- Momper AIDS 2018; Brookie Best personal communication
Darunavir/cobicistat in pregnancy

- Avoid DRV/c and ATV/c 2nd trimester
- No data ATV/c but expect to be similar to DRV/c
- Change to DRV 600 mg/r 100 mg bid or ATV 400/r 100 mg daily

Mirochnik IAS 2018 (abstract)
What about NNRTIs (efavirenz, rilpivirine, doravirine)?

- Rilpivirine (RPV) levels variable among pregnant women
- Total RPV AUC ~ 30 to 40% ↓ during pregnancy vs. postpartum
- Unbound fraction (active) less affected by pregnancy
- ~10% women trough < EC90 (level needed to inhibit 90% replication) but 90% trough = OK
- FDA Oct 2018 Odefsey and Complera label: “For pregnant patients who are already on ARVs before pregnancy and virologically suppressed (HIV-1 VL UD), one tablet taken once daily may be continued. Lower exposures of RPV were observed during pregnancy, therefore viral load should be monitored closely.”
- Efavirenz: okay to start anytime in pregnancy
- No information about doravirine in pregnancy

FDA Oct 2018; Eke JAIDS 2018; Osiyemi Inf Dis Ther 2018; Schalkwijk CID 2017
Preferred Regimens in ART-Naïve Pregnant Women

ABC/3TC or TDF/FTC

- ATV/r
  - Increase dose in 2\textsuperscript{nd} and 3\textsuperscript{rd} trimester

- DRV/r
  - Dose 600/100 mg BID

- RAL
  - BID formulation only

- DTG
  - Avoid preconception/1\textsuperscript{st} trimester
    - Unless effective contraception

No efficacy data with TAF in pregnancy although PK is appropriate
Case Discussion

- MM is a 42 year old male, diagnosed with HIV infection in 1982
- Initially with poor adherence, failed several NRTIs, including AZT, ddI, d4t, nelfinavir
- Complete viral suppression was achieved on darunavir/ritonavir, zidovudine/3TC, efavirenz X 5 years with excellent adherence.
- Review of mutations show only M184V
- He would like to reduce the number of pills (pill burden) he takes.
- Is simplification possible to maintain VL suppression?
Switch Therapy: Reasons to Change ART in VL Suppressed PLWH

- Simplification
  - Reduce number of pills (pill burden)
  - Reduce frequency of administration
  - Address food insecurity
- Improve tolerability and avoid long term toxicity
- Avoid drug-drug interactions
- Manage HCV or other OI infections
- Reduce costs (e.g. fewer inpt/outpt services, lower # rx’s, fewer clinic encounters w/FDC vs > 2 tabs/day)
- Pregnancy
  - Improve adherence

Principles for Switching ART

• Review ARV hx (VL responses, ARV toxicities, cumulative resistance.
• Archived resistance mutations may re-emerge under selective drug pressure, even if not detected in most recent resistance tests.
• Assume resistance if documented failure on ART with lower genetic resistance barrier. (eg. NNRTI, EVG/c, RAL based regimens).
• Do not switch a suppressed ARV regimen unless the new ART is likely as active against resistant virus as the suppressive regimen.
• Within/between class switches appropriate if no prior resistance
• Preliminary data suggest that potent new ARVs may allow VL suppressed pts w/ previous VFIs and certain resistant mutations to switch from 5+ pills/day to simpler regimens with 2 pills/day
• Review co-morbid conditions (e.g. HBV) and drug-drug interactions
• Ensure correct ART regimen is dispensed!!
## Selected Dual-Therapy Switch Regimens for Maintenance Therapy in PLWH with Suppressed VL

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTG + RPV</td>
<td>▪ SWORD-1,2</td>
</tr>
<tr>
<td>DTG + 3TC</td>
<td>▪ ASPIRE* (randomized phase III)[1]</td>
</tr>
<tr>
<td></td>
<td>▪ ANRS 167 LAMIDOL* (single-arm phase II)[2]</td>
</tr>
<tr>
<td>DTG + DRV/r</td>
<td>▪ DUALIS (randomized phase III)[8]</td>
</tr>
<tr>
<td>EVG/c + DRV</td>
<td></td>
</tr>
<tr>
<td>DRV/r + 3TC</td>
<td>▪ DUAL-GESIDA* (randomized phase IV)[9]</td>
</tr>
<tr>
<td>DRV/cobi + RPV</td>
<td></td>
</tr>
<tr>
<td>ATV/r + 3TC</td>
<td>▪ SALT* (randomized phase IV)[11]</td>
</tr>
<tr>
<td></td>
<td>▪ ATLAS-M* (randomized phase IV)[12]</td>
</tr>
<tr>
<td>LA CAB + RPV</td>
<td>▪ ATLAS, FLAIR, ATLAS-2M (randomized phase III)[13-15]</td>
</tr>
<tr>
<td></td>
<td>▪ LATTE-2* (randomized phase IIb)[16]</td>
</tr>
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SWORD 1 & 2: Switch From Suppressive ART to Dolutegravir (DTG) + Rilpivirine (RPV) Dual Therapy

Pts with HIV-1 RNA < 50 c/mL for ≥ 12 mos on 1st/2nd ART regimen 2 NRTIs + INSTI, NNRTI, or PI; no previous VF; HBV negative (N = 1024)

Results:
- HIV-1 RNA < 50 c/mL @ Wk 48 showed noninferiority -0.2%.
- VL suppression maintained to 100 wks.
- Significant improvement in bone turnover markers from baseline to Wk 48 in switch arm.
- Neutral effects on lipid profile.
- Discontinuations due to adverse events (overall: 4%, CNS-related: 2%)

Dolutegravir 50 mg plus Rilpivirine 25 mg (Juluca™)

• Single tablet of NRTI sparing 2 drug regimen
• FDA indication: replaces the current ART if
  • HIV VL <50c/mL on a stable ART for at least 6 months
  • No history of treatment failure and no known resistance
• One tablet daily with food (~ 400 kcal and 13 gm fat)
• If co-administered with rifabutin: add extra 25 mg rilpivirine tablet
• Similar drug interactions as seen with dolutegravir and rilpivirine
• Monitor for increased toxicity if CrCl < 30cc/min
• Not yet ready for initial ART therapy—consider as NRTI sparing regimen

• Phase 3 Open Label (Ongoing), n= 670
• Tx experienced with UD VL > 6 mo ART, no VL failures
• Switched to DOR/3TC/TDF immediately (n=447) or after 24 weeks (n=223) from 2NRTIs plus NNRTI, PI, or INSTI

% with VL < 50 cc/ml

At 24 weeks
• ADRs 19.5% switches vs. 2.2% continued
• More favorable changes in fasting LDL-C and non-HDL-C, lower in DOR vs continued PI ARVs (p<0.0001)

DE. Drugs (2018) 78:1643; Kumar P et al. ID week LB2
Switch From Suppressive ART to Boosted Darunavir/r or ATV/r+ 3TC

- Observational retrospective study
- Changed to dual NRTI
- Proteinuria detected in 38%

n=122 with HIV-1 VL < 50 c/mL mean 3.1 yrs with 2 NRTIs + PI; no previous VF

Results:
- HIV-1 RNA < 50 c/mL @Wk 48 showed noninferiority -0.2%
- Significant improvement in proteinuria
- Neutral effects on lipid profile
- Discontinuations due to adverse events (overall: 4%, CNS-related: 2%)

Capetti AF et al. BMC Infect Dis 2017; 17:658.
Brief HIV/OI Updates

• MAC prophylaxis: DHHS OI and IAS Guidelines
  • **Not recommended** if immediately initiate ART.
  • Recommended if CD4 <50 c/mm³ and not on ART or remain viremic on ART
  • Discontinued if VL fully suppressive d/t minimal risk of MAC (2 R, PC trials)
• Ongoing chronic immune activation and inflammation in PLHIV
  • more likely to develop CV complications, including ASCVD/PAD
What’s in the Future for ART

- Nanosupensions: carbotegravir, rilpivirine, maraviroc
- Fostemsavir
- PRO 140
- PrEP
  - Maraviroc: MVC vs. MCV/TDF vs MCV/FTC vs TDF/FTC X 48 wks showed comparable safety and tolerability as TDF/FTC (n= 88)
  - Dapavirine vaginal ring:
- HIV cure

Carbotegravir (CAB)

• INSTI analogue of dolutegravir
• High potency/efficacy against broad range of HIV resistant strains
• $T_{1/2} = 40$ hr with few drug-drug interactions
• Oral tabs 5, 10, 30, 60 mg; SQ and IM long acting nanosuspensions
• Being studied in combination with NNRTI rilpivirine (RPV).
• Long acting nanosuspensions of RPV are also in clinical development
• Phase I trials: prolonged exposures of both 30 days following IM inj
• May be advantageous for non-adherent pts or those w/ daily pill fatigue.
• No weight gain reported to date in HIV neg persons thru wk 41
LATTE-2: Long-Acting Formulations of Cabotegravir (CAB) + Rilpivirine (RPV) as Maintenance Therapy in PLWH

Induction Phase

CAB 30 mg + ABC/3TC
20 Weeks (n=309)
Plus RPV 25 mg once daily for 4 wks before randomization

If VL < 50 c/ml → Maintenance Phase

CAB 400 mg + RPV 600 mg IM q 4 weeks (n=115)
CAB 600 mg + RPV 900 mg IM q 8 weeks (n=115)
Oral CAB 30 mg + ABC/3TC daily (n=56)

ADR:
- Injection site pain
- Nasopharyngitis
- Diarrhea
- Headache
- High overall patient satisfaction

HIV RNA <50 Copies/mL (%)

48 wks 96 wks

91% 92% 89% 87% 94% 84%

CAB + RPV as Maintenance Therapy: ATLAS and Flair Trials

- Atlas: Phase III, OL, MC trial; n= 618; VL UD >6 mo on 1st/2nd ART; no VL failure
  - LA CAB+ RPV vs SOC ART of 2NRTI+INSTI, NNRTI, or PI.
  - Oral CAB 30 mg + RPV 25 mg daily x 4 wks, IM CAB LA 600 mg/RPV LA 900 mg IM X 1, then CAB LA (400 mg) + RPV LA (600 mg) q 4 wks
  - Results: 93% vs 95% (SoC ART) VL <50 c/ml @wk 48; 75% injection reactions

- Flair: Phase III, OL, MC trial (n=566)
  - TX naive DTG/ABC/3TC oral X 20 wks, if UD VL, randomize to cont oral ART or CAB + RPV as Maintenance Therapy: ATLAS and Flair Trials

References:
**FLAIR: Efficacy at Wk 48**

- Confirmed VF: n = 3 per arm; emergent NNRTI + INSTI resistance in all CAB + RPV failures (all HIV-1 subtype A1), no resistance in DTG/ABC/3TC failures

### Virologic Outcomes (FDA Snapshot)

<table>
<thead>
<tr>
<th></th>
<th>LA CAB + LA RPV (n = 283)</th>
<th>DTG/ABC/3TC (n = 283)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virologic Success (≤ 50 c/mL)</td>
<td>93.6</td>
<td>93.3</td>
</tr>
<tr>
<td>Nonresponse (≥ 50 c/mL)</td>
<td>2.1</td>
<td>2.5</td>
</tr>
<tr>
<td>No Virologic Data</td>
<td>4.2</td>
<td>4.2</td>
</tr>
</tbody>
</table>

### AEs, n (%)

<table>
<thead>
<tr>
<th>AEs occurring in ≥10% of patients</th>
<th>LA CAB + LA RPV (n = 283)</th>
<th>DTG/ABC/3TC (n = 283)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any event (per patient)</td>
<td>246 (87)</td>
<td>225 (80)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>56 (20)</td>
<td>48 (17)</td>
</tr>
<tr>
<td>Headache</td>
<td>39 (14)</td>
<td>21 (7)</td>
</tr>
<tr>
<td>Upper RTI</td>
<td>38 (13)</td>
<td>28 (10)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>32 (11)</td>
<td>25 (9)</td>
</tr>
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### Characteristic to Wk 72

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>LA CAB + LA RPV (n = 283)</th>
</tr>
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<tbody>
<tr>
<td>Patients receiving injections, n</td>
<td>278</td>
</tr>
<tr>
<td>Injections given, n</td>
<td>7704</td>
</tr>
<tr>
<td>ISR events, n (%)</td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>1879 (85.3)</td>
</tr>
<tr>
<td>Nodule</td>
<td>86 (3.9)</td>
</tr>
<tr>
<td>Induration</td>
<td>82 (3.7)</td>
</tr>
<tr>
<td>Swelling</td>
<td>38 (1.7)</td>
</tr>
<tr>
<td>Warmth</td>
<td>38 (1.7)</td>
</tr>
<tr>
<td>Grade 3 ISR pain*</td>
<td>12 (&lt; 1.0)</td>
</tr>
<tr>
<td>Median duration of ISRs, days</td>
<td>3</td>
</tr>
<tr>
<td>ISR pain leading to d/c, n (%)</td>
<td>2 (&lt; 1.0)</td>
</tr>
</tbody>
</table>

**BRIGHTTE: Fostemsavir (FTR) + OBR in Heavily Treatment–Experienced PLWH**

- **Fostemsavir**: prodrug of temsavir, an attachment inhibitor that binds directly to gp120, blocking viral attachment and entry into CD4+ cells.
- Active against CCR5, CXCR4, and dual tropic viruses
- No cross resistance with other ARVs
- BRIGHTTE: R, DB, PC, phase III with 1-2 active ARVs (n= 272)
  - n= 99 OL, no fully active approved ARVs and failing current ART

• Humanized monoclonal Ab binds to CCR5 to block HIV entry
• Weekly SQ injections
• Monotherapy maintenance therapy (short term data) only in ½ of pts
• High genetic barrier to resistance, active against MVC resistant viruses
• No known drug interactions
• CD01 OL (n=31) switched to 350 SQ wkly monotherapy if VL <50. 10/16 maintenance phase w/VL suppressed 47-129 days
• CD02: OL (n=52) tx experienced w/ VL failure, 350 mg SQ/wk added
• CD 03: ongoing R, OL monotherapy (planned n=300) at 350 or 525 mg weekly for 48 wks. Can switch to 525 mg dose if VL failure.
• Potential for monotherapy in selected PLWH

• Latent reservoirs not accessible to ART
• 2 cases of potential “cure” to date:
  • “London pt”s/p stem cell transplant off ART X 18 mo
  • Berlin patient: Timothy Brown—off ART X 12 yrs
  • Both had leukemia and received donor cells with a genetic mutation (CCR5-delta 32) resistant to HIV infection.
• Bone-marrow transplantation unlikely to be a realistic treatment option in the near future d/t chemotherapy
• HIV virus can still enter thru X4 entry way (smaller # of PLWH)
• Future gene directed therapy against CCR5 virus (50% of PLWH).

https://www.nytimes.com/2019/03/04/health/aids-cure-london-patient.html;
https://www.sciencemag.org/news/2019/03/has-second-person-hiv-been-cured
Benefits of Adherence

Barriers to Adherence

- SE from DI b/t HIV meds and co-administered meds
- Trouble swallowing pills
- Difficulty taking pills
- Pill burden, food insecurity
- A busy schedule, shift work, or travel that makes it hard to take medicines on time
- An unstable living or housing situation
- Illness or depression
- Alcohol/drug use interferes with AOLs
- Fear of disclosing one’s HIV+ status
- The cost of HIV medicines

Strategies to Improve Adherence

- Discuss with your PCP whether simplification or change in ART is appropriate.
- Take your medicine at the same time each day.
- Match your medicine schedule to your life. (e.g. brushing your teeth, eating a meal).
- Try a weekly or monthly pill tray to assist whether or not you took your ARVs that day.
- Set an alarm on your clock, watch, or phone for the time to take your ARVs.
- Use a calendar to check off the days you have taken your ARVs.
- Download a free app from the Internet to your computer or on your smartphone to remind you when it’s time to take your ARVs. Search for “reminder apps,” and you will find many choices.
- Ask a family member or friend to help you remember to take your meds.
- Receiving Text or phone messaging from healthcare member.
- Empower patient in his/her care.
Adherence Decreases Over Time

(Ongoing adherence assessment is essential!

(P < .01 for difference between months 1 and 4; months 1 and 8)


Patients reporting 100% adherence, %

- 1 Month: 74%
- 4 Months: 68%
- 8 Months: 65%
• Considerable progress has been achieved in the care of PLWH
• Undetectable HIV VL on ART and PrEP equals untransmittable (U=U)
• INSTI based ART with F/TAF are preferred for initial ART
• TAF is noninferior to TDF for PrEP
• Intermittent PrEP appears effective in MSM only
• Cobicistat and ritonavir boosters can result in different drug interactions and outcome
• Simplification, once daily regimens, and long acting injectables are effective strategies that can increase adherence
• Ending the HIV epidemic and curing HIV are anticipated by 2030
The Clinician Consultation Center is a free telephone advice service for clinicians by clinicians. Receive expert clinical advice on HIV, PrEP, PEP, hepatitis C, substance use and perinatal HIV.

See [ncc.ucsf.edu](http://ncc.ucsf.edu) for more information.

**HIV/AIDS Warmline** 800-933-3413
HIV testing, ARV regimens, resistance, and co-morbidities

**Perinatal HIV Hotline** 888-448-8765
Pregnant women with HIV or at-risk for HIV & their infants

**Hepatitis Warmline** 844-HEP-INFO
HCV testing, monitoring, treatment
* For IHS & VA only

**PrEPline** 855-HIV-PrEP
Pre-exposure prophylaxis for persons at risk of contracting HIV

**Substance Use Warmline** 855-300-3595
Substance use evaluation and management

**PEPline** 888-448-4911
Occupational + non-occupational exposure management
1. Which of the following ARV regimens has been removed from current Antiretroviral Guidelines as an appropriate initial regimen for PLWH (persons living with HIV)?

A. ABC/3TC/dolutegravir (Triumeq)
B. TAF/FTC/bictegravir (Biktarvy)
C. TAF/FTC/Elvitegravir/cobi (Genvoya)
D. TDF/3TC/doravirine (Delstrigo)
E. DTG plus lamivudine
2. Which of the following has been recently associated with the use of integrase inhibitor based therapy?

A. Dyslipidemia
B. Lactic acidosis
C. Myocardial infarction
D. Weight gain
3. Which of the following might occur when changing from a ritonavir boosted darunavir regimen to Symtuza (cobicistat boosted darunavir regimen)?

A. No differences expected since ritonavir equal to cobicistat.
B. Increased risk of CYP3A induction interactions
C. Higher levels of DRV are expected with cobicistat boosting
D. Increased risk of CYP3A 2B6, 2C9, and 2C19 inhibition.
4. Which of the following prophylaxis is no longer recommended in a person with AIDS, VL of 100K c/ml, and CD4 35 cells/mm3, who is starting ART?

A. PCP
B. CMV
C. Toxo
D. MAC
The END: Thank you for Listening
Selected References

Conference on Retrovirus and Opportunistic Infections (CROI 2019) http://retroconference.org/

• AIDS Education and Training Centers National Resource Center http://www.aids-ed.org
• Clinical Care Options HIV : http://www.clinicaloptions.com
• HIV-Associated Resources on the Web. (http://www.iasusa.org)
• DHHS Perinatal HIV Guidelines
• PrEP Watch (http://www.prepwatch.org/)
• Global HIV Prevention (http://www.avac.org/ht/d/sp/i/262/pid/262)
• Please PrEP Me (https://www.pleaseprepme.org/)