HIV Update 2018

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Target Audience: Pharmacists
ACPE#: 0202-0000-18-063-L02-P
Activity Type: Knowledge-based
This activity is supported by an independent educational grant from Merck & Co., Inc.
Disclosures

Betty J. Dong is a HIV consultant for Healthworks.com

The American Pharmacists Association is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.
Learning Objectives

1. Identify important changes in recently updated guidelines that have the potential to influence the management of HIV/AIDS.
2. Summarize 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.
Assessment Question #1:
You are a pharmacist who is giving a hepatitis B vaccine to an HIV+ patient with an undetectable HIV VL and sustains a needle stick. Which of the following is recommended by the CDC to reduce your risk of HIV transmission?

A. Tenofovir DF/emtricitabine plus dolutegravir
B. Tenofovir DF/emtricitabine plus darunavir/ritonavir
C. Tenofovir AF/emtricitabine/evitegravir/cobicistat
D. Zidovudine/lamivudine plus atazanavir/ritonavir
Assessment Question #2:

Which of the following is the most appropriate initial ART recommended by DHHS Guidelines for Most Persons With HIV Infection?

a) Atazanavir/ritonavir plus Abacavir/lamivudine if HLA B5701 neg
b) Elvitegravir/cobicistat plus Tenofovir AF/emtricitabine
c) Efavirenz plus Tenofovir DF/emtricitabine
d) Darunavir/cobicistat plus Tenofovir DF/emtricitabine
Assessment Question #3:

Which of the following patient counseling information should be provided about administration of the Raltegravir HD 600 mg formulation?

A. Take one tablet BID with food
B. Avoid co-administration with proton pump inhibitors
C. Avoid co-administration with calcium antacids
D. Can be changed to chewable or oral suspension if desired
Assessment Question # 4: Which of the following might occur when changing from a ritonavir boosted darunavir regimen to a cobicistat boosted darunavir regimen?

A. No differences are expected since ritonavir is the same as cobicistat
B. Potential risk of ART failure due to lower DRV trough levels
C. Improvement in serum creatinine levels and renal function
D. Increased risk of drug interactions due to CYP3A4 induction
Assessment Question # 5: Joe is a busy business executive who travels a lot and eats when he can. His family members remind Joe to take his medications on a daily basis but his HIV VL remains detectable. Which of the following is the most likely barrier to his ART adherence?

A. HIV stigma  
B. Difficulty swallowing pills  
C. Food insecurity  
D. Unstable housing
Glossary

- ARV = antiretroviral agent
- ART = antiretroviral therapy
- UD VL = undetectable HIV RNA level
- NRTI: nucleoside reverse transcriptase inhibitor
- PI = Protease inhibitor
- NNRTI = non nucleoside reverse transcriptase inhibitor
- INSTI = integrase inhibitor
- /c = cobicistat
- /r = ritonavir
- TDF = tenofovir disoproxil fumarate
- TAF = tenofovir alafenamide
- FTC = emtricitabine
- 3TC = lamivudine
- ABC = abacavir
- DRV/r = darunavir/ritonavir
- ATV/r = atazanavir/ritonavir
- RPV = rilpivirine
- DTG = dolutegravir
- RAL = raltegravir
- EVG/c = elvitegravir/cobicistat
Top Ten Topics Updates

- State of the HIV Epidemic
- Undetectable = Untransmissable
- PrEP vs PEP
- Update in DHHS ART Guidelines
- Single Tablet Regimens
- TDF vs TAF
- All Boosters are not the same: ritonavir vs cobicistat
- HIV drug interactions
- New Agents in the Pipeline
- Adherence
Estimated Annual HIV Infections in US

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

37,600 New HIV Infections in 2014

23% Heterosexuals
8,600 infections
5% People who inject drugs
1,700 infections
3% Gay and bisexual men who inject drugs
1,100 infections

About 1 in 4 new HIV infections is among youth ages 13-24
Most of them do not know they are infected, are not getting treated, and can unknowingly pass the virus on to others

The Need for HIV Prevention: Continued HIV Risk

**Lifetime Risk of HIV Diagnosis by Transmission Group**

- MSM: 1 in 6
- Women Who Inject Drugs: 1 in 23
- Men Who Inject Drugs: 1 in 36
- Heterosexual Women: 1 in 241
- Heterosexual Men: 1 in 473

**Lifetime Risk of HIV Diagnosis among MSM by Race/Ethnicity**

- African American MSM: 1 in 2
- Hispanic MSM: 1 in 4
- White MSM: 1 in 11

Source: Centers for Disease Control and Prevention

HIV Prevention Strategies

Comprehensive Prevention Strategies: condoms, clean needles, safer sex, risk reduction, education

CDC Sept 2017 endorses

**U=U**

Undetectable = Untransmittable
What is Pre-exposure (PrEP) and Post-exposure Prophylaxis (PEP)

- After exposure to HIV, infection may become established.
- **PrEP** (Pre-exposure prophylaxis) is providing ART prophylaxis to an HIV-uninfected/negative person **before** potential HIV exposure.
- **PEP** (Post-exposure prophylaxis) is providing ART to HIV uninfected/negative **after** exposure (start ASAP after exposure) to reduce the chance of infection.
# Tenofovir DF/emtricitabine PrEP Results: Real World Outcomes

<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>Gl: 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>

Case Discussion

- You dispense a new prescription for tenofovir disoproxil fumarate/emtricitabine (Truvada™) one tablet daily to prevent HIV infection. The 28 yr old male patient states that his provider told him he needs to take the medication daily but he has heard that 2:1:1 works just as well.

- What is 2:1:1? How would you address his question and how would you counsel him?
IPERGAY: On-Demand PrEP (2:1:1)

Dosing Schedule: 1 Sexual Event

2 tabs (TDF/FTC or PBO) w/food 2-24 hours before sex

1 tab (TDF/FTC or PBO) 24 hrs later

1 tab (TDF/FTC or PBO) 48 hours later

Monday Tuesday Wednesday Thursday Friday Saturday Sunday

Total tablets = 4 tablets for HIV prophylaxis

“On-demand” regimen constitutes:

• 2 TDF/FTC or PBO 2 - 24 hours with food before sexual exposure
• 1 TDF/FTC or PBO 24 hours and 48 hrs after first dose
• Multiple exposures: one tablet daily until the last exposure, then last 2 tablets
• If< 1 week between exposures, LD=1 tablet only

IPERGAY Results: On-Demand PrEP

- **16 HIV infections**
  - PBO=14 (incidence: 6.6/100 PY)
  - TDF/FTC=2 (incidence: 0.91/100 PY)

- Average 15 pills/month (11-21)

- Adherence: pill counts, TDF/FTC levels
  - 28% did not take TDF/FTC or PBO
  - 43% correct; 29% suboptimal dose
  - No resistance noted

- ADR: TDF/FTC vs PBO: higher GI/renal
  - GI: 14% vs 5% (p=0.002)
  - Renal: 18% vs 10% (p=0.03)

- NNT: 18/year to prevent 1 infection

- 86% reduction (95% CI: 40-98, p=0.002)

IPerGay Findings and Conclusions

- On demand regimen was effective among high-risk MSM with frequent sex (median of 10 sex acts/month and 8 partners every two months).

- Suggest that 3-4 days/week (on average) may be effective.

- Subset of MSM “systematically or often” used PrEP during sex (median of 5 sex acts/month) and took ≤ 15 pills/month. 100% efficacy w/TDF/FTC vs 6 infections in placebo arm but shorter F/U period.

- Cautions and concerns:
  - Is efficacy the same among other high risk persons (e.g. women, IDU)
  - Is less than 4 tabs/week effective long term?
  - Women likely will need 6-7 tablets/week for efficacy

- CDC guidelines recommend daily PrEP dosing

Assessment Question #1:

You are a pharmacist who is giving a hepatitis B vaccine to an HIV+ patient with an undetectable HIV VL and sustains a needle stick. Which of the following is recommended by the CDC to reduce your risk of HIV transmission?

- How common and risky is this exposure?
- What should be done?
HIV Transmission Risks

- Single Contact with contaminated Blood/Body Fluids

- Needle-stick 1/400 (0.23%) to HIV+ source patient (SP)
  - Deep NS
  - Visibly bloody needle
  - High HIV viral load
  - HIV transmission risk less if SP has UD VL

- Needle-sharing IVDU: 0.67% (1/150)

- Blood transfusion before 1985 (HIV-1) and 1992 (HIV-2): HIV risks 1:2,100,000

- Non-intact skin/mucous membrane exposures 1/1000

- No risks: Non-bloody body secretions (e.g. saliva, urine, feces, sweat, tears)

PEP CDC Guidelines; MMWR Recomm Rep 2005;54(RR-9):1-17
Post-Exposure Prophylaxis (PEP)

- Antiretrovirals given *after* risky exposure to prevent HIV
- Occupational PEP
  - After needle-stick, muco-cutaneous or cutaneous exposures to blood or infectious body fluids
- Non-occupational PEP (nPEP):
  - After risky sex/condom breakage, IVDU, sexual assault, found needles
- Evaluate exposure mode, fluid exposed to, HIV status of source patient, and risk factors of source patient.

PEP CDC Guidelines; MMWR Recomm Rep 2005;54(RR-9):1-17
Undetectable HIV Viral Load on Antiretroviral Therapy (ART) Prevents HIV Transmission

- Benefits of offering/Treating All HIV+ with ART:
  - To reduce HIV viral load and infectiousness
  - To reduce risk of HIV transmission to uninfected partner

- HIV Treatment as Prevention:
  - “Test and Treat”: A Public health approach to prevent new HIV transmission
  - SF Dept Public Health and Zuckerberg SF General Hospital “Getting to Zero” Eliminate HIV within 10 years

- NYC 2nd to offer ART to all:
## HIV Transmission Risk with Undetectable HIV VL

<table>
<thead>
<tr>
<th>Trial</th>
<th>Subjects</th>
<th>Outcome</th>
<th>Condoms</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPTN 052 (RC) 5.5 yr F/U¹</td>
<td>1763 heterosexual discordant couples early vs delayed ART</td>
<td>HIV incidence 0.9% (19 early arm and 59 delayed arm; (P &lt; .0001))</td>
<td>Yes; 95%</td>
<td>93% protection, delayed arm and unlinked HIV infxns</td>
</tr>
<tr>
<td>Partners (Observational F/U 1.3 yr³)</td>
<td>548 heterosexual and 340 MSM discordant couples</td>
<td>No HIV infections reported. Estimate risk 0.3-0.7/100c/yr</td>
<td>No</td>
<td>11 unlinked infxns (10 MSM, 1 heterosexual)</td>
</tr>
<tr>
<td>Opposites Attract Study⁴ (Observational 1.5 yr/couple)</td>
<td>358 MSM discordant couples</td>
<td>No HIV infections. 0-1.56/100 CYFU (77.9% UD) 0-1.16/100 CYFU (no condom)</td>
<td>No</td>
<td>3 unlinked HIV infxns</td>
</tr>
</tbody>
</table>

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**CDC Sept 2017 endorses U=U**

**Undetectable = Untransmittable**

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Post-Exposure Prophylaxis (PEP) Evaluation

- Is exposure within the “window” for PEP? No human studies—start ASAP after exposure
  - Within 72 hr (CDC) based on animal data
  - Within 36 hr (NYC) based on same animal data

- Offer vs. recommend PEP
  - Recommend if HIV+ SP (risks ↓ if UD VL)
  - Offer: Risks (ARV toxicity) vs. benefits (~80% risk reduction)

- No infections reported by CDC since 1999 for occupational exposures

- Evaluate risks for HBV and HCV infection

PEP CDC Guidelines; MMWR Recomm Rep 2005;54(RR-9):1-17
PEP Side Effects, DI, and Monitoring

- Side effects:
  - Tenofovir/emtricitabine: GI, headache, renal/bone abnormalities
  - Raltegravir (RAL): myalgias, creatine kinase (rare)
  - Dolutegravir (DTG): CNS: insomnia, headache, anxiety, depression, nightmares/abnormal dreams
  - false ▲ Scr

- Drug interactions: Al++/Mg/Ca cations

- EP Monitoring
  - 4th gen HIV Ag/Ab baseline, 6 wks, 4 mo (if SP HIV/HCV+, 6 mo )
  - CBC, Scr, LFTs baseline, repeat LFTs and Scr 2 weeks and prn
  - HCV Ab baseline, 3 and 6 mo; HCV VL @ 3-6 wks
What is the Current State of Antiretroviral Therapy (ART) and What are the Current Recommendations?

https://aidsinfo.nih.gov/understanding-hiv-aids/infographics
HIV Continuum of Care

HIV Care Continuum, United States, 2014
An estimated 1.1 million people are living with HIV in the United States.

% of all people living with HIV

- Diagnosed: 85%
- Receiving Care: 62%
- Retained in Care: 48%
- Virally Suppressed: 49%

Persons less likely to obtain viral suppression
- AA and Latinos << Whites
- Ages 13 to 25 years of age

2017 DHHS HIV ARV Guidelines

- ART is recommended for all individuals with HIV
  - Regardless of CD4 T lymphocyte cell count
    - Regardless of viral load (eg. elite controllers and low level viremia)
  - To reduce the morbidity and mortality associated with HIV infection
  - To prevent HIV transmission
  - May be deferred b/c clinical and/or psychosocial factors, but should be initiated ASAP
- Willingness and readiness to initiate therapy.

<table>
<thead>
<tr>
<th>Product</th>
<th>Components</th>
<th>Food</th>
<th>CrCL</th>
<th>DI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triumeq™</td>
<td>Dolutegravir 50 mg/Abacavir 600 mg /lamivudine 300 mg if HLA B5701 neg</td>
<td>No</td>
<td>≥50 cc/min</td>
<td>Oct-2</td>
</tr>
<tr>
<td>Genvoya™</td>
<td>Elvitegravir 150/cobicistat 150 mg Tenofovir alafenamide (TAF) 10 mg /Emtricitabine 200 mg</td>
<td>Yes</td>
<td>≥30 cc/min</td>
<td>CYP3A4</td>
</tr>
<tr>
<td>Stribild™</td>
<td>Elvitegravir 150/cobicistat 150 mg Tenofovir disoproxil fumarate (TDF) 300 mg/emtricitabine 200 mg</td>
<td>Yes</td>
<td>≥70 cc/min</td>
<td>CYP3A4</td>
</tr>
<tr>
<td>Stop if &lt;50 cc/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atripla™</td>
<td>Efavirenz 600 mg TDF 300 mg/emtricitabine 200 mg</td>
<td>Empty stomach</td>
<td>≥50 cc/min</td>
<td>CYP3A4</td>
</tr>
<tr>
<td>Compler™</td>
<td>Rilpivirine 25 mg TDF 300 mg/E mtricitabine 200 mg</td>
<td>~ 400 kcal</td>
<td>≥50 cc/min</td>
<td>CYP3A4</td>
</tr>
<tr>
<td>Odefsey™</td>
<td>Rilpivirine 25 mg TAF 25 mg/emtricitabine 200 mg</td>
<td>~ 400 kcal</td>
<td>≥30 cc/min</td>
<td>CYP3A4</td>
</tr>
<tr>
<td>Juluca™</td>
<td>Dolutegravir 50 mg Rilpivirine 25 mg</td>
<td>~ 400 kcal</td>
<td>CYP3A4 OCT-2</td>
<td></td>
</tr>
</tbody>
</table>
Virologic Outcomes in Tx-Naive HIV+ Pts by ART Pill Burden and Regimen Class

- More pts on STR vs MTR achieved viral suppression, fewer experienced rebound
- STRs associated with increased likelihood of viral suppression vs MTRs in multivariate analysis
  - aHR for all regimens: 1.38 (95% CI: 1.30-1.46); aHR for NNRTI-based regimens: 1.23 (95% CI: 1.04-1.44); aHR for INSTI-based regimens: 1.01 (95% CI: 0.92-1.12)

<table>
<thead>
<tr>
<th>Virologic Outcomes</th>
<th>STR (n = 5542)</th>
<th>MTR (n = 3648)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-1 RNA &lt; 50 c/mL during initial ART, %</td>
<td>70.3</td>
<td>54.4</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Median time to first VL &lt; 50 c/mL, mos (IQR)</td>
<td>4.0 (2.2-6.2)</td>
<td>4.2 (2.3-7.1)</td>
<td>.003</td>
</tr>
<tr>
<td>≥ 1 VL after BL, %</td>
<td>88.3</td>
<td>83.2</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Among pts with ≥ 1 VL, suppression never achieved, %</td>
<td>20.3</td>
<td>34.6</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Rebound 1 (1 VL&gt; 200 c/mL after suppression + d/c), %</td>
<td>3.7</td>
<td>4.8</td>
<td>.01</td>
</tr>
<tr>
<td>Rebound 2 (2 VLs &gt; 200 c/mL after suppression), %</td>
<td>4.8</td>
<td>6.1</td>
<td>.005</td>
</tr>
<tr>
<td>Among pts with ≥ 1 VL, rebound 1 or 2, %</td>
<td>12.1</td>
<td>20.0</td>
<td>&lt; .0001</td>
</tr>
</tbody>
</table>

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
- Initial ART Treatment
- Toxicity Short Term Long Term
When to Start ART? Benefits and Risks of Rapid ART Starts

- **Definition of rapid ART:** starting within 14 days of HIV diagnosis.

- **Benefits**
  - Increased viral suppression at 12 mo: RR 1.17, 95% confidence interval (CI) 1.07–1.27
  - In care at 12 mo (RR 1.11, 95% CI 0.99–1.26)
    - Likelihood of starting ART within 90 days (RR 1.35, 95% CI 1.13–1.62)
    - Likelihood of starting ART 12 months after eligibility was established (RR 1.17, 95% CI 1.07–1.27).
  - Nonsignificant
    - Reduced mortality (RR 0.53, 95% CI 0.24–1.08)
    - Loss to follow-up at 12 months (RR 0.66, 95% CI 0.42–1.04).

- **Barriers to Starting:**
  - Insufficient time to disclose and accept HIV (stigma)
  - Seek partner approval (pregnant)
  - Uncertainty about test results
  - Confirmatory HIV testing

- **Acceptability of Starting ART**
  - MSM 28.4% (US) to 97.7% (Thailand)

Ford N et al AIDS 2018, 32:17–23
San Francisco Experience: Same-Day Observed ART Initiation Versus Standard of Care ART (SOC)

- Significantly shorter time to UD VL ($P<0.0001$) vs SOC ART (2010-2013)
- Similar safety/tolerability as SOC ART (DTG, RAL, EVG/cDRV/r)

Case Discussion

- GP is a 48 yr old female with new HIV infection, CD4 400 c/mm³, HIV RNA 260K, HLA B5701 negative, interested in starting ART. She states she is interested in one pill once daily

- PMH
  - Hx IDU – buprenorphine
  - HCV, Genotype 1a, treatment naïve
  - Renal insufficiency CrCL 50-60 cc/min
  - Hypertension—enalapril and amlodipine
  - GERD—omeprazole 40 mg daily

- What ART Regimens would you recommend for her? What changes if any in her current medications would be needed to start ART?
### DHHS Guidelines: Initial ART = Integrase Inhibitor Based Regimens Recommended for Most People with HIV

<table>
<thead>
<tr>
<th>Integrase Inhibitor (INSTI)</th>
<th>PLUS 2 Nucleoside Reverse Transcriptase Inhibitors (NRTIs)</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dolutegravir 50 mg</td>
<td>Abacavir/lamivudine only if HLA B5701 neg</td>
<td>One tablet daily (Triumeq™)</td>
</tr>
<tr>
<td>Dolutegravir 50 mg</td>
<td>Tenofovir disoproxil fumarate (TDF)/emtricitabine (Truvada™) OR Tenofovir alafenamide (TAF)/emtricitabine (Descovy™)</td>
<td>Two tabs daily</td>
</tr>
<tr>
<td>Elvitegravir/cobicistat</td>
<td>Tenofovir disoproxil fumarate (TDF)/emtricitabine</td>
<td>One tablet daily (Stribild™) w/ food</td>
</tr>
<tr>
<td>Elvitegravir/cobicistat</td>
<td>Tenofovir alafenamide (TAF)/emtricitabine</td>
<td>One tablet daily (Genvoya™) w/ food</td>
</tr>
<tr>
<td>Raltegravir HD 1200 mg daily (2 X 600 mg tabs) or RAL 400mg bid</td>
<td>Tenofovir disoproxil fumarate (TDF)/emtricitabine (Truvada™) OR Tenofovir alafenamide (TAF)/emtricitabine (Descovy™)</td>
<td>Three tablets daily</td>
</tr>
</tbody>
</table>

Why Are Integrase Inhibitor (INSTI) Based ART Preferred for Initial ART?

- Efficacy comparable to boosted PI regimens
- Single pill formulations available
- High genetic barrier to resistance (e.g. dolutegravir)
- Minimal potential for drug interactions, especially with HCV DAA
- Well tolerated
- Neutral impact on CV, metabolic, and lipids
Dolutegravir (Tivicay™)

- FDC with abacavir/lamivudine (Triumeq™) only if HLA B5701 neg
- Virologic suppression was similar/superior to INSTI, NNRTI and PI
- Higher genetic barrier than raltegravir or elvitegravir; rare baseline resistance
- Given once daily with/without food
  - Food: ↑66% levels with high fat meal
- Lower DTG AUC if CrCL < 30 cc/min; not cleared by dialysis
- Inhibits OCT2 → ↓tubular secretion creatinine; mean ↑Scr 0.1-0.3 mg/dL (4 wks)
- Well tolerated; neuropsychiatric symptoms (similar to efavirenz) reported
- 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 in 6 to 12 mo (range 3 to 6%)
- Onset 3.1 mo
  - Risk factors: Females HR (2.64), Age > 60yr (HR 2.86), using ABC (HR 2.42)
  - Reversible after D/C (n=6 re-challenge with recurrence in all)

## Selected Dolutegravir Drug Interactions Requiring Adjustments

<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) Antacids, laxatives, sulcrafate, buffered meds</td>
<td>Concurrent Al+ Mg+ antacids ↓ DTG AUC 76% vs 26% if staggered. Fasting: DTG AUC ↓ 37%-39% with CA+ ↓ 54% to 57% iron Food: normal AUC</td>
<td>Administer Al++, Mg++, or Ca++-antacids, laxatives, iron, sulcrafate six hours before or <strong>two</strong> hours after DTG Take DTG and calcium supplements or iron <strong>together</strong> 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>

## Selected Dolutegravir 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% when co-administered with multivitamin.</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>Hepatitis C direct acting agents (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>Enalapril, amlodipine</td>
<td>No interactions</td>
<td>Standard DTG dosage</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>$\downarrow$ DTG</td>
<td>Avoid co-administration, 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 2017; Liverpool HCV drug interaction
### Raltegravir HD (Isentress HD™) 600 mg Film Tablets

<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</td>
<td>1200 mg (600 mg X 2) once daily with or without food</td>
<td>Not interchangeable with chewable or oral suspension</td>
</tr>
<tr>
<td>Pediatric WT &gt; 40kg</td>
<td></td>
<td></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>400 mg BID</td>
<td>HD dosing not available</td>
</tr>
</tbody>
</table>

- 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 reactions, myositis

ONCEMRK: RAL 1200 mg Daily Noninferior to RAL 400 mg BID at Wk 48

- 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

<table>
<thead>
<tr>
<th>Medication</th>
<th>Interaction</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al-Mg containing antacids</td>
<td>RAL Cmin ↓ 49% to 63%</td>
<td>Avoid with RAL 400 mg tabs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Consider Ca-containing antacids</td>
</tr>
<tr>
<td>CA-containing antacids</td>
<td>RAL HD Cmin ↓ 48% to 57%</td>
<td>Do not co-administer with RAL HD 1200 mg once daily.</td>
</tr>
<tr>
<td>Rifampin</td>
<td>↓ RAL</td>
<td>Give RAL 800 mg bid. Avoid with RAL HD 1200 mg tabs</td>
</tr>
<tr>
<td><strong>Anticonvulsants</strong></td>
<td><strong>↓ RAL</strong></td>
<td>Co-administration not recommended</td>
</tr>
<tr>
<td>Buprenorphine, enalapril, omeprazole, amlodipine, DAA HCV</td>
<td>No interaction</td>
<td>Standard RAL dosing</td>
</tr>
</tbody>
</table>

Raltegravir package insert, Liverpool HIV drug interaction website
## Fixed Dose Once Daily Evitegravir/cobicistat Combinations

<table>
<thead>
<tr>
<th>Product</th>
<th>Components</th>
<th>Dosage/Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genvoya™</td>
<td>Elvitegravir 150/cobicistat 150 mg</td>
<td>One tab with food</td>
</tr>
<tr>
<td></td>
<td>Tenofovir AF 10 mg/Emtricitabine 200 mg if CrCL &gt; 30 cc/min</td>
<td>Diarrhea, nausea</td>
</tr>
<tr>
<td>Stribild™</td>
<td>Elvitegravir 150/cobicistat 150 mg</td>
<td>One tablet with food</td>
</tr>
<tr>
<td></td>
<td>Tenofovir DF 300 mg/emtricitabine 200 mg if CrCL &gt; 70 cc/min. Stop if CrCL&lt;50 cc/min</td>
<td>Diarrhea, nausea</td>
</tr>
</tbody>
</table>

### Medication Interaction Recommendation

<table>
<thead>
<tr>
<th>Medication</th>
<th>Interaction</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amlodipine</td>
<td>Amlodipine 3A4 metabolism. Elvitegravir/cobicistat↑amlodipine exposure~2-fold.</td>
<td>consider a 50% amlodipine dose reduction</td>
</tr>
<tr>
<td>Buprenorphine,</td>
<td>No interaction</td>
<td>Standard dosing</td>
</tr>
<tr>
<td>enalapril,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>omeprazole,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>most DAA HCV</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Liverpool Drug Interaction Website
Comparing Tenofovir Disoproxil Fumarate (TDF) and Tenofovir Alafenamide (TAF)

TAF results in 80-90% lower TFV plasma levels

OAT, organic anion transporter; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TFV, tenofovir.

TAF is a Substrate of the Intestinal P-gp Transporter
Lower TAF Dose 10 mg in a Boosted Regimen

Intestinal P-gp transporter pumps drugs (e.g. TAF) back into the intestinal lumen. Cobicistat inhibits intestinal P-gp transporter allowing greater TAF absorption.

COBI, cobicistat
BCRP, breast cancer resistance protein
P-gp, permeability glycoprotein 1
RTV, ritonavir

Van Gelder et al. Drug Metab Dispos. 2002, 30:924;
Babusis et al. Mol Pharmaceutics. 2013, 10:459.
Summary: Differences Between Tenofovir AF (TAF) and Tenofovir disoproxil fumarate (TDF)?

- TAF is prodrug of tenofovir
- TAF has 90% lower tenofovir concentrations than TDF
  - Less renal and bone toxicity
- Significantly ↑ LDL levels (17–26 mg/dL change) vs TDF regimens (3–4 mg/dL change)
- Drug interactions:
  - P-gp, BCRP, OATP1B1, and OATP1B3 substrate.
  - Reduced TAF levels with pgp inducers: avoid enzyme inducers (tipranavir/r, rifampin, rifabutin, St. John’s wort, anticonvulsants (Pb, phenytoin, carbamazepine, oxcarbazepine)
- 70% TDF vs 1% TAF urinary excretion (80% TAF metabolized)

Descovy package insert; Corado KC & Daar ES. Expert Opin Pharmacother 2017:18:4, 427
Effect of EVG/cobicistat vs ritonavir on Tenofovir DF Levels

- TDF Cmin were higher with EVG/c than when TDF was paired with boosted PI’s, NNRTIs, or non-boosted INSTIs
- ↑ TDF Cmin women, older age, lower wt
- Higher probability stopping TDF in the first year with EVG/c (43.6%) vs. boosted PI (15.6%), NNRTI (13.1%), or INSTI (10.6%)
- When TAF is used with boosters, dose =10 mg but no correction is done for TDF, ↑ Increased risk of TDF renal insufficiency
- US: TAF 25 mg/FTC; UK 10 mg/FTC

Cattaneo JAIDS 2018 Jan 1,77:86
GS-1089: Switch From TDF- to TAF-Containing ART Noninferior at Wks 48 and 96

- Phase III trial of pts with HIV-1 RNA < 50 c/mL, eGFR ≥ 50 mL/min while receiving FTC/TDF + third ARV (N = 663)

Virologic Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Wk 48</th>
<th>Wk 96</th>
</tr>
</thead>
<tbody>
<tr>
<td>FTC/TAF (n = 333)</td>
<td>94</td>
<td>93</td>
</tr>
<tr>
<td>FTC/TDF (n = 330)</td>
<td>89</td>
<td>89</td>
</tr>
</tbody>
</table>

Overall Treatment Difference (95% CI)

- Wk 48: Favors FTC/TAF
- Wk 96: Favors FTC/TDF


GALLANT_JE_Another way to say FTC/TDF
GS-1089: Bone and Renal Parameters for TAF- vs TDF-Containing ART at Wk 48


↑ proteinuria with TDF
Case Discussion

- GP is a 48 yr old female with new HIV infection, CD4 400 c/mm³, HIV RNA 260K, HLA B5701 negative, interested in starting ART. She states she is interested in one pill once daily.

- PMH
  - Hx IDU – buprenorphine
  - HCV, Genotype 1a, treatment naïve
  - Renal insufficiency CrCL 50-60 cc/min
  - Hypertension– enalapril and amlodipine
  - GERD—omeprazole 40 mg daily

What ART Regimens would you recommend for her if GP wishes to “cure” her HCV infection?
<table>
<thead>
<tr>
<th>ARV(s)</th>
<th>GLE/PIB</th>
<th>SOF/VEL</th>
<th>SOF/VEL/VOX</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATV + (RTV or COBI)</td>
<td>X</td>
<td>✓*</td>
<td>X</td>
</tr>
<tr>
<td>DRV + (RTV or COBI)</td>
<td>X</td>
<td>✓*</td>
<td>✓*†</td>
</tr>
<tr>
<td>LPV + RTV</td>
<td>X</td>
<td>✓*</td>
<td>X</td>
</tr>
<tr>
<td>EFV</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>RPV</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>DTG</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>RAL</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>EVG/COBI/FTC/TDF</td>
<td>✓*†</td>
<td>✓*</td>
<td>✓*†</td>
</tr>
<tr>
<td>EVG/COBI/FTC/TAF</td>
<td>✓†</td>
<td>✓</td>
<td>✓†</td>
</tr>
<tr>
<td>3TC/ABC</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>TAF</td>
<td>✓</td>
<td>✓</td>
<td>✓†</td>
</tr>
<tr>
<td>TDF</td>
<td>✓</td>
<td>✓*</td>
<td>✓*†</td>
</tr>
</tbody>
</table>

*Monitor for tenofovir toxicity if used with TDF. †No clinically significant drug interaction per prescribing information; AASLD/IDSA and DHHS guideline recommend monitoring liver enzymes owing to lack of clinical safety data.

### DHHS 2017 Guidelines: Initial ART: Protease Inhibitor Based Regimens Recommended In Certain Clinical Situations

<table>
<thead>
<tr>
<th>Protease Inhibitor (PI)</th>
<th>PLUS 2 Nucleoside Reverse Transcriptase Inhibitors (NRTIs)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darunavir 800 mg plus</td>
<td>Tenofovir DF/emtricitabine (Truvada) OR Tenofovir AF/emtricitabine (Descovy) OR Abacavir/lamivudine (Epzicom) <strong>Only if HLAB5701 neg</strong></td>
<td>DRV preferred if concern about transmitted resistance or adherence - sulfa moiety - best tolerated of the PI - GI-n/diarrhea</td>
</tr>
<tr>
<td>- ritonavir 100 mg OR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- 150 mg cobicistat</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Prezcobix)</td>
<td>Tenofovir DF/Truvada</td>
<td></td>
</tr>
<tr>
<td>- Daily with food</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atazanavir 300 mg plus</td>
<td>Abacavir/lamivudine (Epzicom) <strong>Only if HLAB5701 neg</strong></td>
<td>ATV less tolerated vs DRV - no sulfa moiety - lower CV events and less progression of atherosclerosis (e.g. carotid artery intima medial thickness) hyperbilirubinemia/jaundice renal stones avoid renal failure</td>
</tr>
<tr>
<td>- ritonavir 100 mg OR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- cobicistat 150 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Evotaz)</td>
<td>Tenofovir DF/Truvada</td>
<td></td>
</tr>
<tr>
<td>- Daily with food</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DHHS ART Guidelines 2017
Question: Is Cobicistat Boosting The Same as Ritonavir Boosting?

- Important PK differences which may lead to different drug interactions
- Ritonavir:
  - Inhibits CYP3A4, 2D6, 2C19, 2C8, 2C9, p-glycoprotein (pgp), BCRP, OATPs, MATE1
  - *induces* CYP1A2, 2B6, 2C9, 2C19 and uridine glucuronosyltranferase (UGT)
- Cobicistat
  - Inhibits CyP3A, 2D6, pgp, BRCP, OATP1B1, OATP1B3, MATE1
  - No induction properties

Switching from Ritonavir to Cobicistat; Potential Effects of Ritonavir Induction (n=12) on Dolutegravir

- Cobi ↑ DTG Cmin 100% vs /r No change in ScR;
- Mech: ? d/t ritonavir induction
- Considerations:
  - Use Cobi if want ↑DTG in renal insufficiency or food insecurity, non-adherence, DTG resistance
  - Use RTV when: want ↓ DTG d/t DTG ADR

From: Effects of ritonavir and cobicistat on dolutegravir exposure: when the booster can make the difference
J Antimicrob Chemother | © The Author 2017. Published by Oxford University Press on behalf of the British Society for Antimicrobial Chemotherapy. All rights reserved. For Permissions, please email: journals.permissions@oup.com.
Does Changing from DRV/r to DRV/c (Prezcobix™) and ATV/r to ATV/c (Evotaz™) Provide Same Virological Efficacy?

- ATV/c appears comparable to ATV/r.
- Faster decay DRV levels with DRV/c vs DRV/r.
- DRV levels below effective Ctrough 30 hr after DRV/c dosing in 11/16 healthy volunteers.
- Cmin DRV/c (31% lower than /r) may be less forgiving than DRV/r for missed/delayed doses.
- Monitor for low level viremia after change to DRV/c.

Elliott et al. J. Antimicrob Chemother 2017;72:2035
### Drug Interaction Differences b/t Cobicistat and Ritonavir Boosting: Some examples

<table>
<thead>
<tr>
<th>Interacting Agent</th>
<th>Cobicistat</th>
<th>Ritonavir</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sertraline/ Bupropion</td>
<td>No changes with cobicistat</td>
<td>↓ AUC with PI/r</td>
<td>Ritonavir induction</td>
</tr>
<tr>
<td>Warfarin</td>
<td>↑ INR</td>
<td>↓ INR</td>
<td>Ritonavir induction</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>rosvastatin 10 mg po X1 and EVG/c ↑rosvastatin AUC 38%, Cmax 89% and Cmin 43%</td>
<td>rosvastatin 10 mg once daily and DRV/r ↑rosvastatin AUC 48%, Cmax144%.</td>
<td>Differences in 3A4 inhibition</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>↑AUC 127%; avoid co-administration</td>
<td>No effect</td>
<td>Ritonavir mixed effects on induction and inhibition of P-gp</td>
</tr>
</tbody>
</table>

- **Take home message:** ritonavir and cobicistat may not provide same interactions
- **Cobicistat lacks enzyme induction properties**
- **Requires 1-2 weeks for enzyme induction to occur and subside**
- **Check all interactions when changing between cobicistat and ritonavir**

DHHS ART Guidelines 2017, Liverpool drug interaction website
### DHHS Guidelines: NonNucleoside Reverse Transcriptase Inhibitors Recommended In Certain Clinical Situations as Initial ART

<table>
<thead>
<tr>
<th>Product</th>
<th>Components</th>
<th>Food</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atripla™</td>
<td>Efavirenz 600 mg/TDF 300 mg/emtricitabine 200 mg</td>
<td>Empty stomach</td>
<td>CrCL &gt; 50 cc/min</td>
</tr>
<tr>
<td>Sustiva™ plus Descovy™</td>
<td>Efavirenz 600 mg TAF 25 mg/emtricitabine 200 mg</td>
<td>Empty stomach</td>
<td>CrCl &gt; 30 cc/min</td>
</tr>
<tr>
<td>Complera™</td>
<td>Rilpivirine 25 mg TDF 300 mg/Emtricitabine 200 mg</td>
<td>~ 400 Kcal</td>
<td>Avoid PPI, HIV VL &lt; 100K, CD4 &gt; 200c/m3; CrCL &gt; 50 cc/min</td>
</tr>
<tr>
<td>Odefsey™</td>
<td>Rilpivirine 25 mg TAF 25 mg/emtricitabine 200 mg</td>
<td>~ 400 kcal</td>
<td>Avoid PPI; HIV VL &lt; 100K, CD4 &gt; 200c/m3; CrCL &gt; 30 cc/min</td>
</tr>
</tbody>
</table>

- Transmitted resistance more likely, low genetic barrier; avoid if no baseline GT
- RPV/TAF/FTC is smallest FDC if there are swallowing issues
- Risk QT prolongation with EFV, RPV
- Less lipid issues with RPV

DHHS ART Guidelines 2017, Complera and Odefsey package inserts
ART Regimens for Initial Therapy When NRTIs Cannot Be Used

- Situations in which one may consider avoiding abacavir, tenofovir AF, and tenofovir DF
  - HLA-B*5701 positive
  - High risk of cardiovascular disease
  - Significant renal impairment

- Regimens with sufficient data to support use as initial therapy when abacavir, tenofovir AF, or tenofovir DF cannot be used
  - Darunavir/r + raltegravir only if HIV RNA <100,000 copies/mL and CD4 >200 cells/mm3.
  - Lopinavir/r + lamivudine

**ART and Pregnancy Updates**

- Restriction of efavirenz use before 8 weeks’ gestation has been removed. Women who become pregnant on suppressive and tolerated efavirenz-containing regimens should continue their current regimens.

- TDF/FTC is preferred and ZDV/3TC is an alternative NRTI

- EFV, RAL, RPV, or BID DRV/RTV can be continued during pregnancy

- Dolutegravir is alternative for naïve pregnant women

- Avoid Elvitegravir/cobicistat based on data showing inadequate levels of both drugs during the 2nd and 3rd trimester as well as viral breakthroughs. If continued, close monitoring is recommended.

New Formulations and New Strategies

- Juluca (dolutegravir plus rilpivirine)
- Bictegravir
- Switch Therapies
Why Consider Changing Therapy in Virologically Suppressed Pts:

- To simplify regimen
  - Reduce number of pills
  - Reduced frequency of administration
  - Address food insecurity
- To improve adherence
- To manage or prevent drug toxicity
- To prevent or manage drug interactions
- To treat HCV or other OI coinfection
- To plan for pregnancy
- To reduce cost
Dolutegravir 50 mg plus Rilpivirine 25 mg (Juluca)

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

<table>
<thead>
<tr>
<th>Product</th>
<th>Components</th>
<th>Food</th>
<th>CrCL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symtuza (UK)</td>
<td>Darunavir 800 mg/Cobicstat 150 mg/Tenofovir AF 10 mg/emtricitabine 200 mg</td>
<td>Yes</td>
<td>&gt; 30cc/min</td>
</tr>
<tr>
<td></td>
<td>Bictegravir 50 mg/TAF 25 mg/emtricitabine 200 mg</td>
<td>No</td>
<td>&gt; 30cc/min</td>
</tr>
<tr>
<td>Triumeq</td>
<td>Dolutegravir 50 mg/Abacavir 600/Lamivudine 300 mg</td>
<td>No</td>
<td>&gt; 50cc/min</td>
</tr>
<tr>
<td>Genvoya</td>
<td>Elvitegravir 150/cobicistat 150 mg/Tenofovir alafenamide 10 mg/Emtricitabine 200 mg</td>
<td>Yes</td>
<td>&gt;30cc/min</td>
</tr>
<tr>
<td>Stribild</td>
<td>Elvitegravir 150/cobicistat 150 mg/Tenofovir DF 300 mg/emtricitabine 200 mg</td>
<td>Yes</td>
<td>≥70cc/min. Stop if &lt;50</td>
</tr>
<tr>
<td>Atripla</td>
<td>Efavirenz 600 mg/TDF 300 mg/emtricitabine 200 mg</td>
<td>Empty stomach</td>
<td>≥50cc/min</td>
</tr>
<tr>
<td>Complera</td>
<td>Rilpivirine 25 mg/TDF 300 mg/Emtricitabine 200 mg</td>
<td>~ 400 Kcal</td>
<td>≥50 cc/min</td>
</tr>
<tr>
<td>Odefsey</td>
<td>Rilpivirine 25 mg/TAF 25 mg/emtricitabine 200 mg</td>
<td>~ 400 Kcal</td>
<td>≥30 cc/min</td>
</tr>
</tbody>
</table>
Darunavir/cobicistat/emtricitabine/tenfovir alafenamide (DRV/c/FTC/TAF)

- First darunavir-based, single-tablet for HIV treatment
- NDA submitted, date of approval unclear. (approved in UK as Symtuza)

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

- Treatment-naive pts with HIV-1 RNA (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 mos on boosted PI + FTC/TDF for ≥ 6 mos; no previous VF on DRV; eGFR ≥ 50 mL/min (N = 1141)
- Switch to DRV/COBI/FTC/TAF (n = 763)
- Continue Boosted PI + FTC/TDF (n = 378)

AMBER: DRV/COBI/FTC/TAF vs DRV/COBI + FTC/TDF for Treatment-Naive Pts

- 1 treatment-emergent resistance mutation (M184I/V) observed in DRV/COBI/FTC/TAF arm
- Similar low rates of grade 3/4 AEs between treatment groups
- Lower rate of AE-related d/c for DRV/COBI/FTC/TAF vs DRV/COBI + FTC/TDF (1.9% vs 4.4%)
- Hip/spine BMD changes more favorable with DRV/COBI/FTC/TAF
- Significantly higher eGFR by serum creatinine ($P < .0001$) and cystatin c ($P = .001$) with DRV/COBI/FTC/TAF

**Wk 48 Virologic Efficacy**

<table>
<thead>
<tr>
<th></th>
<th>DRV/COBI/FTC/TAF (n = 362)</th>
<th>DRV/COBI + FTC/TDF (n = 363)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pts (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VIROLOGIC SUCCESS*</td>
<td>91.4</td>
<td>88.4</td>
</tr>
<tr>
<td>HIV-1 RNA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.4 (n = 16)</td>
<td>3.3 (n = 12)</td>
</tr>
</tbody>
</table>

*Primary endpoint: HIV-1 RNA < 50 c/mL by FDA snapshot.

EMERALD: Switch From Boosted PI + FTC/TDF to DRV/COBI/FTC/TAF in Suppressed Pts

- No PI or NRTI resistance mutations (VL resistance data: n = 1 DRV/COBI/FTC/TAF; n = 3 control)
- Similar low rates of grade 3/4 AEs, d/c for AEs between treatment groups
- Significant improvements in hip/spine BMD for DRV/COBI/FTC/TAF vs control
- Similar eGFR by serum creatinine between groups (P = .092); increased eGFR by cystatin c with DRV/COBI/FTC/TAF (P = .034)
- Post-hoc subanalysis, improved bone and renal parameters after switch

Wk 48 Virologic Efficacy

- Treatment difference: 1.2% (95% CI: -1.7% to 4.1%)
- Treatment difference: 0.4% (95% CI: -1.5% to 2.2%)

Virologic Success*

94.9
93.7

DRV/COBI/FTC/TAF (n = 763)
Continue Boosted PI + FTC/TDF (n = 378)

Virologic Rebound†

2.5
2.1

Pts (%)

0
20
40
60
80
100

*HIV-1 RNA < 50 c/mL (FDA Snapshot).
†Primary endpoint: confirmed HIV-1 RNA ≥ 50 c/mL or premature d/c with last HIV-1 RNA ≥ 50 c/mL.

**Bictegravir (formerly GS-9883)**

- Co-formulated as a FDC bictegravir 50 mg/TAF 25 mg/emtricitabine 200 mg—FDA approval expected Feb 2018
- Potent INSTI; no boosting required
- High barrier to resistance, including some DTG resistant strains
- Half-life = 16 to 20 hr
- Once daily with or without food
- Hepatic metabolism: CYP3A4 and UGT1A1 substrate
- High virologic efficacy and good tolerability up to 48 wks
- Low potential for drug interactions but affected by 3A4 inducers/inhibitors

https://aidsinfo.nih.gov/drugs/570/bictegravir/o/professional
Bictegravir (BIC) Drug Interaction Profile

<table>
<thead>
<tr>
<th>Interaction Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BIC is a substrate of UGT1A1 and CYP3A4</strong></td>
<td>BIC does not inhibit nor induce either</td>
</tr>
<tr>
<td><strong>Inhibitor of both</strong></td>
<td>ATV is the only known dual inhibitor (BIC exposure ↑ 315%)</td>
</tr>
<tr>
<td>- UGT1A1 and CYP3A4</td>
<td></td>
</tr>
<tr>
<td><strong>Inducer of both</strong></td>
<td>Rifabutin is a weak dual inducer (BIC exposure ↓ 38%)</td>
</tr>
<tr>
<td>- UGT1A1 and CYP3A4</td>
<td></td>
</tr>
<tr>
<td><strong>Inhibitor</strong></td>
<td>BIC exposures ↑ 61-74% with CYP3A4 inhibitors voriconazole and DRV/COBI</td>
</tr>
<tr>
<td>- CYP3A4</td>
<td></td>
</tr>
<tr>
<td><strong>Inducer</strong></td>
<td>Rifampin ↓ BIC AUC 75% (B/F/TAF BID with rifampin is underway)</td>
</tr>
<tr>
<td>- CYP3A4, UGT1A1, P-gp</td>
<td></td>
</tr>
<tr>
<td>- Antacids</td>
<td>Dose BIC ≥ 2 hours before or after antacids</td>
</tr>
<tr>
<td>- Metformin</td>
<td>metformin exposure ↑ 39% but no dose adjustments are required</td>
</tr>
</tbody>
</table>

ATV, atazanavir; AUC, area under the concentration-time curve; CYP, cytochrome P450; PK, pharmacokinetics; UGT, UDP-glucuronosyltransferase
Bictegravir + FTC/TAF vs DTG + FTC/TAF: Wk 24 and 48 Efficacy

Phase 3, R, DB, MC trial (n= 629)

- HIV VL < 50c/ml Wk 48
  - BIC 50 mg/FTC/TAF (n = 314): 99.3%
  - DTG + FTC/TAF (n = 315): 97.7%
  - Treatment difference: 0.7% (95% CI: -1.4 to 2.8; p=0.43)

Phase 2, DB, R, MC trial (n=98)

- HIV VL < 50c/ml Wk 24
  - BIC 75 mg/FTC/TAF (n=65): 96.9%
  - DTG + FTC/TAF (n=33): 93.9%
  - Treatment difference: 2.9% (95% CI: -8.5% to 14.2%)

Bictegravir + FTC/TAF vs DTG + FTC/TAF: AEs and Lab Abnormalities

<table>
<thead>
<tr>
<th>Any Grade AE Occurring in ≥ 5% in Either Arm, %</th>
<th>BIC + FTC/TAF (n = 65)</th>
<th>DTG + FTC/TAF (n = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Nausea</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>Headache</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>URTI</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Chlamydial infection</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Back pain</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Furuncle</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Flatulence</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Costochondritis</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Hemorrhoids</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Pruritus</td>
<td>0</td>
<td>6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade 2-4 Lab Abnormality ≥ 5% in Either Arm, %</th>
<th>BIC + FTC/TAF (n = 64*)</th>
<th>DTG + FTC/TAF (n = 32*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatine kinase</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>AST</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td>ALT</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>LDL</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Amylase</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Hematuria</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Glycosuria</td>
<td>2</td>
<td>6</td>
</tr>
</tbody>
</table>

*Pts with ≥ 1 post-BL laboratory assessment, excluding those not specified for all pts.

Difficult to conclude on safety from small study, but 4 fully enrolled phase III trials now evaluating efficacy, safety, tolerability of coformulated BIC/FTC/TAF

What’s in the Future for ART

- Nanosupensions: carbotegravir, rilpivirine
- Doravirine
- Fostemsavir
- Ibalizumab
- PrEP
  - Tenofovir alafenamide (TAF) Discover comparing TAF to TDF—results in 2020
  - 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:

Gulick R et al. Ann Intern Med. 8/22/17
Carbotegravir

- INSTI analogue of dolutegravir
- High potency and efficacy against broad range of HIV resistant strains
- T1/2 = 40 hr with few drug-drug interactions
- Formulations: oral tabs 5, 10, 30, 60 mg; SQ and IM long acting nanosuspensions
- Being studied in combination with NNRTI rilpivirine.
- Long acting nanosuspensions of rilpivirine are also in clinical development
- Phase I trials show prolonged exposures of both 30 days following IM injections
- May be advantageous for non-adherent patients or those with daily pill fatigue.

LATTE-2: Long-Acting Formulations of Cabotegravir + Rilpivirine as Maintenance Therapy in HIV Infected Persons

Induction Phase
- Cabotegravir 30 mg + ABC/3TC for 20 Weeks (n=309)
- Plus rilpivirine 25 mg once daily for 4 wks before randomization

If VL < 50 c/ml → Maintenance Phase
- Cabotegravir 400 mg + Rilpivirine 600 mg IM every 4 weeks (n=115)
- Cabotegravir 600 mg + Rilpivirine 900 mg IM every 8 weeks (n=115)
- Oral Cabotegravir 30 mg + ABC/3TC daily (n=56)

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

HIV RNA <50 Copies/mL (%)

<table>
<thead>
<tr>
<th></th>
<th>48 wks</th>
<th>96 wks</th>
</tr>
</thead>
<tbody>
<tr>
<td>91%</td>
<td>92%</td>
<td>89%</td>
</tr>
<tr>
<td>87%</td>
<td>94%</td>
<td>84%</td>
</tr>
</tbody>
</table>

Doravirine (MK-1439-007)

- Investigational potent nonnucleoside (NNRTI) in phase 3 clinical trials
- Formulations: single-drug tablet and FDC tablet = doravirine plus tenofovir DF and lamivudine
- Administration with or without food
- Metabolized by CYP3A4; not a CYP450 inhibitor or inducer
- Active in vitro against mutations resistant to other NNRTI (efavirenz, rilpivirine): K103N, Y181C, G190A, E101K, E138K, K103N/Y181C
- Side effects: dizziness, nightmares, depression (less than efavirenz).

Doravirine Is Noninferior to DRV + RTV at Wk 48 (FDA Snapshot)

- Multicenter, randomized, double-blind phase III trial in ART-naive pts with HIV-1 RNA $\geq 1000$ c/mL (N = 769)
- Efficacy similar in both arms regardless of baseline HIV-1 RNA or CD4+ cell count
- No drug resistance detected in pts with PDVF through Wk 48 in either arm
  - n = 1 pt with noncompliance discontinued at Wk 24, developed DOR and FTC resistance


Slide credit: clinicaloptions.com
TMB-301: Long-Acting Ibalizumab in Pretreated Pts Infected With Multidrug-Resistant HIV

- Ibalizumab: humanized mAb to conformational epitope on CD4 receptor that blocks post-attachment HIV entry into CD4+ T-cells without altering normal cell function
- Single-arm, open-label phase III trial
  - Primary endpoint: \( \geq 0.5 \log_{10} \) HIV-1 RNA decrease at Day 14

Pts with HIV-1 RNA > 1000 copies/mL; on ART ≥ 6 mos, on stable ART ≥ 8 wks; resistant to ≥ 1 ARV from 3 classes, sensitive to ≥ 1 ARV for OBR (N = 40)

Control period: Days 0-7

Primary endpoint: Day 14

Wk 25

Ibalizumab 2000 mg IV Day 7 (Loading Dose) Continue Failing ART Days 0-14

Ibalizumab 800 mg IV Day 21, Q2W (Maintenance Dose) Switch to OBR Day 14

TMB-301: Efficacy, Safety of Ibalizumab Through 24 Wks

- Primary endpoint: 83% with $\geq 0.5 \log_{10}$ HIV-1 RNA decrease at Day 14 vs 3% at end of control period ($P < .0001$)
  - 60% with $\geq 1.0 \log_{10}$ HIV-1 RNA decrease
  - Mean decrease by Day 14: $1.1 \log_{10}$

- 9 pts reported 17 serious AEs
  - 1 drug-related serious AE (IRIS) resulted in discontinuation
  - 9 other pts discontinued
  - Death (n = 4; liver failure, Kaposi sarcoma; end-stage AIDS, lymphoma)
  - Consent withdrawal (n = 3)
  - Lost to follow-up (n = 2)

- No cases of anti-ibalizumab antibodies

<table>
<thead>
<tr>
<th>Wk 24 Virologic Outcome</th>
<th>Ibalizumab + OBR</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\geq 1.0 \log_{10}$ HIV-1 RNA decrease, %</td>
<td>55</td>
</tr>
<tr>
<td>$\geq 2.0 \log_{10}$ HIV-1 RNA decrease, %</td>
<td>48</td>
</tr>
<tr>
<td>HIV-1 RNA &lt; 50 copies/mL, %</td>
<td>43</td>
</tr>
<tr>
<td>HIV-1 RNA &lt; 200 copies/mL, %</td>
<td>50</td>
</tr>
<tr>
<td>Mean HIV-1 RNA decrease from baseline, $\log_{10}$</td>
<td>1.6</td>
</tr>
</tbody>
</table>

TMB-311: Ibalizumab + OBR in Treatment-Experienced Pts With Multidrug Resistance

- **Ibalizumab**: investigational humanized mAb to CD4 receptor second extracellular domain, blocking postattachment viral entry (active vs CXCR4 and CCR5 tropic virus, no known cross-resistance with current ARVs)

- TMB-311 evaluated efficacy and safety of ibalizumab + OBR through Wk 48 in treatment-experienced US pts with MDR completing 24-wk TMB-301 trial (n = 27)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TMB-311 Pts (n = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, yrs</td>
<td>53</td>
</tr>
<tr>
<td>Median HIV-1 RNA, log_{10} c/mL</td>
<td>4.3</td>
</tr>
<tr>
<td>Median CD4+ cell count, cells/mm³</td>
<td>102</td>
</tr>
</tbody>
</table>

Virus resistance, n (%)
- Exhausted ≥ 3 ARV classes       16 (59)
- Exhausted ≥ 4 ARV classes       9 (33)
- Resistant to all approved ARVs   4 (15)

### TMB-311: Efficacy and Safety Outcomes With Ibalizumab Through Wk 48 Expanded Access

- CD4+ cell count increases to Wk 24 maintained at Wk 48
- 24 out of 27 pts (89%) completed study through Wk 48
  - D/c for consent withdrawal (n = 2), AE unrelated to treatment (n = 1)
- No anti-ibalizumab antibodies detected

<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>
</tbody>
</table>

**Wk 24 viral suppression rate, %** (N = 40)
- HIV-1 RNA < 50 c/mL: 43
- HIV-1 RNA < 200 c/mL: 50

**Wk 48 viral suppression rate, %** (n = 27)
- HIV-1 RNA < 50 c/mL: 59
- HIV-1 RNA < 200 c/mL: 63

**Mean CD4+ cell count increase from BL to Wk 24, cells/mm³**: 62

---

**Treatment-Emergent AE,* %**

<table>
<thead>
<tr>
<th>TMB-311 Pts (n = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infection</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Rash</td>
</tr>
</tbody>
</table>

*All mild to moderate.

---

BRIGHTE: Fostemsavir + OBR in Heavily Treatment-Experienced Pts

- **Fostemsavir**: prodrug of investigational attachment inhibitor temsavir
- **BRIGHTE**: ongoing randomized, double-blind, placebo-controlled phase III trial with open-label extension (N = 371 treated pts)
  - Includes nonrandomized cohort with same eligibility criteria (except no remaining ARV classes and no remaining fully active approved drugs) given FTR 600 mg BID + OBR during open-label extension (n = 99)

HIV-infected pts experiencing failure of current ART, HIV-1 RNA ≥ 400 c/mL, with 1-2 remaining ARV classes (≥ 1 fully active available agent/class), not able to construct viable regimen with remaining agents (n = 272)

https://aidsinfo.nih.gov/drugs/508/fostemsavir--fostemsavir/0/professional
BRIGHTE: Efficacy and Safety Outcomes With Fostemsavir

- Primary endpoint: adjusted* mean HIV-1 RNA log_{10} change at Day 8 in randomized ITT-E population
  - FTR vs PBO: -0.79 vs -0.17 (difference: -0.625; 95% CI: -0.810 to -0.441; \( P < .0001 \)†)

- Wk 24 viral suppression by snapshot
  - Randomized cohort (N = 272):
    - HIV-1 RNA < 40 c/mL: 54%
    - HIV-1 RNA < 200 c/mL: 71%
  - Nonrandomized cohort (N = 99):
    - HIV-1 RNA < 40 c/mL: 36%

- Most common grade 2-4 tx-related AEs were nausea, diarrhea, headache, vomiting, fatigue, asthenia

<table>
<thead>
<tr>
<th>Wk 24 Safety Event, n (%)</th>
<th>Randomized Cohort (n = 270)</th>
<th>Nonrandom. Cohort (n = 99)</th>
<th>All Treated Pts (N = 371)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any event</td>
<td>243 (90)</td>
<td>93 (94)</td>
<td>338 (91)</td>
</tr>
<tr>
<td>Grade 2-4 tx-related AE</td>
<td>49 (18)</td>
<td>19 (19)</td>
<td>68 (18)</td>
</tr>
<tr>
<td>AE leading to d/c</td>
<td>12 (4)</td>
<td>9 (9)</td>
<td>21 (6)</td>
</tr>
<tr>
<td>Serious AE</td>
<td>73 (27)</td>
<td>37 (37)</td>
<td>112 (30)</td>
</tr>
<tr>
<td>Tx-related serious AE</td>
<td>6 (2)</td>
<td>3 (3)</td>
<td>9 (2)</td>
</tr>
<tr>
<td>Death†</td>
<td>8 (3)</td>
<td>9 (9)</td>
<td>17 (5)</td>
</tr>
</tbody>
</table>

*Mean adjusted by HIV-1 RNA on Day 1. †Per Levene’s test of homogeneity of variance. ‡12 out 17 deaths from AIDS-related events; 1 death from recurrent atypical mycobacterial infection due to IRIS.

https://aidsinfo.nih.gov/drugs/508/fostemsavir--fostemsavir/0/professional
Benefits of Adherence

- Side effects: drug interactions between HIV meds and other meds
- Trouble swallowing pills/difficulty taking pills
- Pill burden, food insecurity
- A busy schedule, shift work, or travel away from home that makes it hard to take medicines on time
- Having an unstable living or housing situation
- Illness or depression
- Alcohol or drug use that interferes with the activities of daily life
- Fear of disclosing one’s HIV+ status
- The cost of HIV medicines

**TIPS FOR TAKING YOUR HIV MEDS, ON TIME, ALL THE TIME**

**ONE DAY, TWO FRIENDS MET IN A COFFEE SHOP...**

**HEY MARC, MY DOCTOR SAYS I NEED TO BE BETTER ABOUT STICKING TO MY HIV REGIMEN. HOW DO YOU DO IT?**

**DO YOU USE A PILL BOX?**

**YEAH, I USE A PILL BOX BUT I STILL HAVE TROUBLE REMEMBERING TO TAKE MY MEDS.**

**IT HELPS ME KEEP TRACK OF THE MEDICINE I NEED TO TAKE THAT DAY.**

**WELL, THERE ARE SOME OTHER THINGS YOU COULD TRY!**

**KEEP YOUR HIV MEDICINES WHERE YOU’LL NOTICE THEM, BUT OUT OF THE REACH OF CHILDREN.**

**CONNECT TAKING MEDICINES TO YOUR DAILY ROUTINE. FOR EXAMPLE, TAKE YOUR MEDS WHEN YOU BRUSH YOUR TEETH.**

**DON’T RUN OUT OF YOUR MEDICINES. REFILL YOUR PRESCRIPTION WHEN YOUR SUPPLY GETS LOW.**

**GET AN ALARM ON YOUR PHONE. I USE THE AIDSinfo DRUG APP.**

**ASK A FRIEND OR FAMILY MEMBER TO REMIND YOU.**

**HEY DID YOU TAKE YOUR MEDS TODAY?**

**THAT’S FINE WHEN I’M AT HOME — BUT WHAT HAPPENS WHEN I HAVE TO WORK LATE OR MY SCHEDULE CHANGES?**

**KEEP A BACK-UP SUPPLY OF YOUR MEDICINE IN YOUR BAG OR AT WORK, SO YOU CAN TAKE YOUR PILLS WHEREVER YOU ARE. AND WHEN YOU TRAVEL, BRING MORE MEDICINE THAN YOU THINK YOU’LL NEED IN CASE YOUR PLANS CHANGE.**

**REMEMBER TO KEEP ALL YOUR APPOINTMENTS WITH YOUR DOCTOR.**

**FOR MORE INFORMATION ON ADHERENCE, GO TO AIDSinfo.**

**IF YOU’RE REALLY STRUGGLING, YOUR DOCTOR CAN GIVE YOU SOME MORE TIPS ON HOW TO STICK TO YOUR HIV REGIMEN. JUST ASK!**
Strategies to Improve Adherence

- Take your medicine at the same time each day.
- **Match your medicine schedule to your life.** Add taking your medicines to things you already do each day, like brushing your teeth or eating a meal.
- **Try a weekly or monthly pill tray** with compartments for each day of the week to help you remember whether or not you took your medicine that day.
- **Set an alarm** on your clock, watch, or phone for the time you take your medicines.
- **Use a calendar** to check off the days you have taken your medicines.
- **Download a free app** from the Internet to your computer or on your smartphone that can help remind you when it’s time to take your medicines. Search for “reminder apps,” and you will find many choices.
- **Ask a family member or friend** to help you remember to take your medicine.
- **Receiving Text or phone messaging** from healthcare member
- **Empower patient in his/her care**

My Strategies to Improve Adherence: Starting ART

- Discuss relationship between adherence and viral load efficacy
- Provide patient education about missed doses; need to stop all ARVs rather than stop selectively.
- Show them the size of the pills and the pill burden of the regimens, take with/without food, optimal times of administration (2 hr window).
- Do not start unless receive all ART from pharmacy
- Anticipate and explain how to manage initial side effects and drug interactions.
- Confirm understanding of regimen
- Provide a mediset or other adherence reminders/aids
Adherence Decreases Over Time

Ongoing adherence assessment is essential!

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

Assessing Adherence: After Initiation of Therapy: Helpful and Not So Helpful Questions

- Helpful Questions: open ended, exploratory
  - “Do you believe the medicines are working for you?”
  - “What concerns do you have about your ARVs?”
  - “What reminders do you use to help remember?”
  - “How do you manage/control side-effects?”
  - “What do you find most difficult about taking your medications?”
  - “How many pills have you missed in last 3 days
  - “What causes you to miss pills?
  - “What are barriers to taking your medications? What do you think would be most helpful to resolve these barriers?”

- Not so helpful Questions
  - “You’re taking your medications aren’t you?”
  - “You haven’t missed any doses have you?”
  - “You are not having any side effects, are you?”
  - “You don’t want to die, do you?”
  - Don’t you understand that you need to take the meds to live?
  - What is your problem?
Conclusions

- HIV infected persons can have close to normal life expectancy.
- Start ART ASAP after HIV diagnosis if the patient is willing/adherent
- An undetectable HIV VL, PrEP, and PEP can reduce HIV transmissions
- Integrase based therapy is recommended as initial therapy due to its efficacy, tolerability, and low risk of drug interactions.
- Protease inhibitors and nonnucleoside reverse transcriptase inhibitor based regimens can be recommended in certain clinical situations
- Pharmacists can improve HIV care by counseling patients about HIV prevention, ensuring optimal ART therapy, and providing effective strategies to foster adherence.
Assessment Question #1:
You are a pharmacist who is giving a hepatitis B vaccine to an HIV+ patient with an undetectable HIV VL and sustains a needle stick. Which of the following is recommended by the CDC to reduce your risk of HIV transmission?

A. Tenofovir DF/emtrictabine plus dolutegravir
B. Tenofovir DF/emtricitabine plus darunavir/ritonavir
C. Tenofovir AF/emtricitabine/evitegravir/cobicistat
D. Zidovudine/lamivudine plus atazanavir/ritonavir
Assessment Question #2:

Which of the following is the most appropriate initial ART recommended by DHHS Guidelines for Most Persons With HIV Infection?

a) Atazanavir/ritonavir plus Abacavir/lamivudine if HLA B5701 neg
b) Elvitegravir/cobicistat plus Tenofovir AF/emtricitabine
c) Efavirenz plus Tenofovir DF/emtricitabine
d) Darunavir/cobicistat plus Tenofovir DF/emtricitabine
Assessment Question #3:

Which of the following patient counseling information should be provided about administration of the Raltegravir HD 600 mg formulation?

A. Take one tablet BID with food
B. Avoid co-administration with proton pump inhibitors
C. Avoid co-administration with calcium antacids
D. Can be changed to chewable or oral suspension if desired
Assessment Question # 4: Which of the following might occur when changing from a ritonavir boosted darunavir regimen to a cobicistat boosted darunavir regimen?

A. No differences are expected since ritonavir is the same as cobicistat
B. Potential risk of ART failure due to lower DRV trough levels
C. Improvement in serum creatinine levels and renal function
D. Increased risk of drug interactions due to CYP3A4 induction
Assessment Question # 5: Joe is a busy business executive who travels a lot and eats when he can. His family members remind Joe to take his medications on a daily basis but his HIV VL remains detectable. Which of the following is the most likely barrier to his ART adherence?

A. HIV stigma
B. Difficulty swallowing pills
C. Food insecurity
D. Unstable housing
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 [nccc.ucsf.edu](http://nccc.ucsf.edu) for more information.

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

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

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

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

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

**PEPline** 888-448-4911
Occupational + non-occupational exposure management
Selected References

- National HIV Curriculum (University of Washington) https://www.hiv.uw.edu/
- Conference on Retrovirus and Opportunistic Infections (CROI 2018) http://retroconference.org/
- Clinical Care Options HIV: http://www.clinicaloptions.com
- HIV Insite: http://hivinsite.ucsf.edu
- HIV-Associated Resources on the Web. (http://www.iasusa.org)
- PrEP Watch (http://www.prepwatch.org/)
- Global HIV Prevention (http://www.avac.org/ht/d/sp/i/262/pid/262)
- Updated Guidelines for Antiretroviral Postexposure Prophylaxis After Sexual, Injection Drug Use, or Other Nonoccupational Exposure to HIV—United States, 2016
The END: Thank you for Listening