Objectives

1. Review pharmacology basics.
2. List ARV agents and examine their mechanisms of action.
3. Examine dose, adverse effects, drug interactions, and special considerations of ARVs in recommended regimens.
HIV Life-cycle

**Recommended Regimens**

- **TDF/FTC or TAF/FTC**
  - TDF/FTC not recommended if CrCl < 70 & TAF/FTC not recommended if CrCl < 30
  - **If HLA-B*5701 is negative**
  - ***If pre-treatment HIV RNA < 100,000 copies/mL & CD4 > 200 cells/mm³**

- **ABC/3TC**

**Alternative Regimens**

- **TDF/FTC or TAF/FTC**
  - **If HLA-B*5701 is negative**
  - ***If pre-treatment HIV RNA < 100,000 copies/mL & CD4 > 200 cells/mm³**

**Lightening Fast Pharmacology Review**

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* TDF/FTC not recommended if CrCl < 70 & TAF/FTC not recommended if CrCl < 30
** If HLA-B*5701 is negative
*** If pre-treatment HIV RNA < 100,000 copies/mL & CD4 > 200 cells/mm³

http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf
Pharmacology Review

- **PK**: What your body does to the drug.
  - Study & characterization of time course of drug
    Absorption, Distribution, Metabolism, & Excretion.
- **PD**: What the drug does to your body.
  - Subjective (anxiety level) or objective (BP, pupil size)

PK Parameters

- **AUC** (area under the curve): average drug concentration over a time period (e.g., 1 dosing interval or 1 day). Represents drug exposure.
- **T½ (half-life)**: time taken to reduce the concentration by 50%
- **Cmax**: Peak plasma concentrations; can be associated with a PD response
- **Cmin**: Plasma concentrations at the end of the dosing interval (just before next dose); lowest concentration within a dosing interval
  - Cmin, Ctrough, Ct (tau: the length of the dosing interval)

Excretion

Transporters

- **P-glycoprotein (P-gp)**: efflux enzyme that "pushes" drugs out of GI blood stream back into GI lumen
  - P-gp inhibitor: RTV, COBI
  - P-gp inducer: SJW, GFJ, rifampin
- **Organic anion transporters (OAT)**: involved in secretion or reabsorption of drugs; in kidney, brain, & liver
  - OAT inhibitor: COBI
- **Organic cation transporters (OCT)**: involved in secretion or reabsorption of drugs; in liver, skeletal muscle, kidney, heart, small intestine, prostate
  - OCT inhibitor: RTV, DTG
Cytochrome P450 Enzymes

- Essential for metabolism of two-thirds of meds cleared by metabolism
- >50 enzymes; however, 6 metabolize 90% of drugs: CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, & CYP3A5
- Primary cause of the majority of drug-drug & drug-food interactions

CYP450 Inducers: ↑CYP450 enzyme activity by ↑enzyme synthesis (e.g., efavirenz, rifampin)

CYP450 Inhibitors: Block metabolic activity of CYP450 enzymes (e.g., protease inhibitors)

Question #1: How quickly does CYP450 induction occur?

1. 1-2 hours
2. 1-2 days
3. 1-2 weeks
4. 1-2 months
CYP450 Inducers

- Onset gradual (1-2 weeks)
- Onset depends on half-life ($t_{1/2}$) of the inducer & synthesis of new enzymes
- Offset depends on inducer elimination & decay of enzyme stores

Question #2: How quickly does CYP450 inhibition occur?

1. 1-2 hours
2. 1-2 days
3. 1-2 weeks
4. 1-2 months

CYP450 Inhibitors

- Onset is rapid (after 1-2 doses)
- Extent of inhibition depends on dose & binding ability of inhibitor
- Offset depends on elimination of the inhibitor & half-life of the inhibitor at enzyme site
- All PIs are net inhibitors of CYP3A4
- **Boosting:** use of low-dose CYP450 inhibitor to ↑ARV exposure

Boosting

- Taking advantage of a drug-drug interaction
- Low-dose CYP450 inhibitors (e.g., RTV or COBI) lead to:
  - ↑AUC, ↑Cmin & ↑Cmax
  - ↓ risk of drug resistance
  - Can use lower doses of PI
  - May eliminate food restriction
  - ↑plasma half-life ($t_{1/2}$)
  - ↓ dosing frequency
Drawbacks of Boosting

- ↑ potential of drug-drug interactions
- ↑ pill-burden
- except fixed-dose combos LPV/r, EVG/c, DRV/c, ATV/c
- ↑ risk of metabolic AEs

However,
- Boosting with RTV or COBI is recommended for PI- & EVG-based regimens

Question #3: Which of the following is (are) true re: RTV & COBI

1. Both inhibit P-gp & BCRP transporters
2. Both inhibit MATE1 & OATP transporters
3. Both result in increased Scr & TG
4. Both inhibit or induce CYP450 enzymes
5. Options 1, 2, & 3
6. All of the above

RTV vs COBI

<table>
<thead>
<tr>
<th></th>
<th>RTV</th>
<th>COBI (Structural analogue of RTV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boosting w/ 100mg QD-BID</td>
<td>Boosting w/ 150mg QD</td>
<td></td>
</tr>
<tr>
<td>Antiviral activity at higher doses</td>
<td>Without antiviral activity</td>
<td></td>
</tr>
<tr>
<td>Inhibits or induces drug-metabolizing enzymes → DDIs</td>
<td>Inhibits drug-metabolizing enzymes → DDIs</td>
<td></td>
</tr>
</tbody>
</table>


RTV vs COBI: PK

<table>
<thead>
<tr>
<th></th>
<th>RTV</th>
<th>COBI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption</td>
<td>Both inhibit intestinal transporters P-gp &amp; BCRP.</td>
<td>↑ absorption of ATV, DRV, TAF</td>
</tr>
<tr>
<td>Excretion</td>
<td>Both inhibit OATP &amp; MATE1 (transporter involved in tubular secretion of Cr)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>↑ Scr due to inhibition of Cr secretion vs. impairment of renal function</td>
<td></td>
</tr>
<tr>
<td></td>
<td>COBI results in higher Scr vs. RTV, may be due to COBI accumulating in tubular cells &amp; having higher concentrations to inhibit MATE1</td>
<td></td>
</tr>
</tbody>
</table>

RTV vs COBI: PK
interchangeable as CYP3A inhibitors

<table>
<thead>
<tr>
<th>Metabolism</th>
<th>RTV</th>
<th>COBI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibition</td>
<td>CYP3A inhibitor</td>
<td>More specific CYP3A inhibitor</td>
</tr>
<tr>
<td></td>
<td>CYP2D6 inhibitor</td>
<td>Weaker CYP2D6 inhibitor</td>
</tr>
<tr>
<td>Induction</td>
<td>CYP1A2, CYP2B6, CYP2C9, &amp; CYP2C19 &amp; glucuronidation inducer</td>
<td>Unlikely to induce drug metabolism</td>
</tr>
</tbody>
</table>


RTV vs COBI: DDIs
Summary of differences in predicted interaction profiles:

<table>
<thead>
<tr>
<th>Meds that are…</th>
<th>RTV</th>
<th>COBI</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucuronidated &amp;/or metabolized by inducible CYPs &amp; w/o CYP3A involvement</td>
<td>↓</td>
<td>not affected</td>
<td>Bupropion or methadone (CYP2B6)</td>
</tr>
<tr>
<td>Glucuronidated &amp;/or metabolized by inducible CYPs to a larger extent than CYP3A</td>
<td>↓</td>
<td>moderately</td>
<td>Sertraline (2B6&gt;2C9, 2C19, 2D6, 3A4)</td>
</tr>
<tr>
<td>Subject to CYP induction or inhibition</td>
<td>↓ or ↑</td>
<td>only ↑</td>
<td>Duloxetine (2D6, 1A2)</td>
</tr>
</tbody>
</table>

- Inducible CYPs: CYP1A2, CYP2B6, CYP2C9, & CYP2C19
- ELV: inducer of CYP2C9 (ELV/c overall effect: ↓ warfarin)


RTV vs COBI: AEs

<table>
<thead>
<tr>
<th>RTV</th>
<th>COBI</th>
</tr>
</thead>
<tbody>
<tr>
<td>D, HA, N, nasopharyngitis</td>
<td>N, D, HA, nasopharyngitis</td>
</tr>
<tr>
<td>Median ↑TG: 32, TC: 9 mg/dL</td>
<td>Median ↑TG: 19, TC: 5 mg/dL</td>
</tr>
<tr>
<td>Median ↑Scr: 0.09 mg/dL; ↓CrCl: 9 mL/min</td>
<td>Median ↑Scr: 0.13 mg/dL; ↓CrCl: 13 mL/min</td>
</tr>
<tr>
<td>D/C due to renal AEs: 1.4%</td>
<td>D/C due to renal AEs: 1.7%</td>
</tr>
</tbody>
</table>


Case #1
**Case #1**

You would like to start ART for your 45 y/o White female patient. She would like a once-daily regimen. She has normal liver and kidney function. She has no ARV drug resistance at baseline and has never taken ARVs.

**Labs:**
- VL=178K copies/mL
- CD4⁺=458 cells/mm³
- HLA-B5701+

**Meds:**
- ethinyl estradiol/norethindrone
- metformin
- calcium/vitamin D

**Allergies:** sulfa (mild rash)

**Factors to consider when selecting a regimen**

- Drug resistance testing
- History of ARV use & prior drug resistance tests
- Comorbidities*
  - Factors potentially influencing adherence*
- Drug adverse effects and allergies
- Drug-drug interactions
- Pregnancy (or pregnancy potential)
- Labs (renal/hepatic function, HLA-B5701, CD4⁺, VL, co-receptor tropism, lipids, etc.)

**Factors to consider in Case #1…**

- Drug resistance testing: no drug resistance
- History of ARV use & prior drug resistance tests: none
- Comorbidities: diabetes
- Drug adverse effects & allergies: no known, sulfa allergy
- Drug-drug interactions: Ca/vit D, metformin, & OC
- Pregnancy: not pregnant
- Labs: HLA-B5701+, CD4⁺=458, VL=178K, nml renal & liver
- Factors potentially influencing adherence: no known, would like QD regimen

**Comorbidities & factors influencing adherence**

- CVD
- Liver/renal disease
- GERD
- Age-related issues (e.g., polypharmacy, vision loss)
- Neurocognitive issues (e.g., cognitive impairment, dementia, psychosis)
- Psychosocial issues (e.g., depression, unstable anxiety, homelessness, incarceration, low social support, stressful life events)
- Active drug & alcohol use
- Health illiteracy & HIV IQ
- Younger age
- Difficulty with taking medication (e.g., trouble swallowing pills)
- Cost and insurance coverage issues
- Convenience (pill burden, dosing frequency, food requirements, etc.)
Nucleos(t)ide Reverse Transcriptase Inhibitors

- Hypersensitivity reaction (HSR)
  - ~8% of patients; usually in 6 weeks of initiation
  - ≥2 of: fever, rash, GI (N/V/D, pain), constitutional (fatigue, achiness), respiratory (dyspnea, cough, pharyngitis)
  - May lead to anaphylaxis, organ failure, & death
  - D/C & NEVER rechallenge: ABC allergy in medical record
  - Standard of care: HLA-B*5701 PRIOR TO ABC USE
  - Does not need to be renally dosed

Abacavir

- Renal insufficiency
  - Risk factors: advanced HIV disease, longer treatment history, nephrotoxic drugs, & pre-existing renal impairment
  - Monitor renal function
  - ↑monitoring frequency if proteinuria, ↓GFR, DM, or HTN
  - Decrease BMD
    - DEXA screening for postmenopausal women & men ≥50 years
    - Switch ART for those with low BMD or osteoporosis taking TDF
  - Used for treatment of HBV

Tenofovir Disoproxil Fumarate

- Renal insufficiency
- Monitor renal function
- ↑monitoring frequency if proteinuria, ↓GFR, DM, or HTN
- Decrease BMD
- DEXA screening for postmenopausal women & men ≥50 years
- Switch ART for those with low BMD or osteoporosis taking TDF
- Used for treatment of HBV

TAF (Tenofovir Alafenamide)

- TDF & TAF require conversion to active drug tenofovir (TFV) diphosphate
- TDF is converted to TFV in blood, then taken up into lymphocytes, macrophages, & other cells, where it is phosphorylated.
- TAF is delivered as TAF to lymphocytes & macrophages, then converted to TFV.
- TFV plasma levels are lower (~90%) with TAF vs. TDF, & TFV levels are higher within lymphocytes.
- As effective as TDF in virologic suppression but less kidneys & bone toxicity

Abacavir

- Take 1 tablet (300mg) orally twice daily with or without food
- Take 2 tablets (600mg) orally once daily AM PM

Tenofovir Disoproxil Fumarate

- Take one tablet (400mg) orally once daily with or without food AM PM
TAF FDC
In 3 FDCs:
1. TAF/FTC: Descovy
   - Cousin of Truvada (TDF/FTC)
   - TAF dose= 25mg
2. TAF/FTC/RPV: Odefsey
   - Cousin of Complera (TDF/FTC/RPV)
   - TAF dose= 25mg
3. TAF/FTC/ELV/c: Genvoya
   - Cousin of Stribild (TDF/FTC/ELV/c)
   - TAF dose= 10mg

TAF & Renal Impairment
- Open-label study of virologically suppressed adults w/ stable eGFRCG (30-69 mL/min), switched from TDF- or non-TDF-containing regimens to E/C/F/TAF
  - Of N=242, 65% were on TDF-containing regimens prior to switch
  - By 96wks, minimal change in eGFR

TAF & HD
- N=5 w/baseline eGFR<50 d/c’ed study drug for ↓CrCl, none w/proximal renal tubulopathy & all w/ risk factors for renal disease progression (HTN & DM)
- Those on TDF at baseline had significant improvements in proteinuria & albuminuria
  - Prevalence of significant proteinuria & albuminuria decreased from 42% to 18% & 49% to 28%, respectively
- Hip & spine BMD increased significantly
- Data support efficacy & safety of QD E/C/F/TAF in eGFR 30-69 mL/min without dose adjustment

E/C/F/TAF & HD
https://clinicaltrials.gov/show/NCT02600819
**Lamivudine**  
- Treatment of HIV & HBV

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamivudine, 1TC</td>
<td>1 tablet (150mg) orally twice daily with or without food</td>
<td>AM, PM</td>
</tr>
<tr>
<td>Lamivudine, 3TC</td>
<td>1 tablet (100mg) orally once daily with or without food</td>
<td></td>
</tr>
</tbody>
</table>

**Emtricitabine**  
- Fluorinated analog of 3TC

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emtricitabine, FTC</td>
<td>1 capsule (200mg) orally once daily with or without food</td>
<td>AM, PM</td>
</tr>
</tbody>
</table>

**Question #4:** What is your current clinical practice for your patients on TDF?  
1. Changing them to TAF  
2. Changing them to ABC  
3. Continuing TDF and monitoring  
4. Something else

**Integrase Inhibitors**

**Raltegravir**  
- Little effect on lipids & glucose  
- AE: rash & HSR, ↑CK, myositis, rhabdomyolysis  
- Few drug-drug interactions  
  - Does not inhibit or induce CYP3A4, UGT1A1, or P-gp  
  - Eliminated by UGT1A1; therefore w/ rifampin, ↑dose to 800mg bid

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raltegravir, RAL</td>
<td>1 tablet (400mg) orally twice daily with or without food</td>
<td>AM, PM</td>
</tr>
</tbody>
</table>
Elvitegravir/Cobi

- EVG: inducer of CYP2C9; metabolized by CYP3A
- Cobi
  - Cobi inhibitor of CYP3A, CYP2D6, P-gp, oat; metabolized by CYP3A
  - inhibits tubular secretion of Cr \( \uparrow \) Scr & \( \downarrow \) CrCl w/o \( \downarrow \) gfr
  - \( \downarrow \) CrCl, U. glucose, U. protein, & phos before & during tx
  - initiation not recommended if CrCl \( < 70 \) mL/min
  - Closely monitor \( \uparrow \) in Scr of \( \geq 0.4 \) mg/dL from baseline
  - D/C EVG/Cobi/TDF/FTC if CrCl \( \downarrow \) to \( < 50 \) mL/min
  - Common AEs: diarrhea, nausea, headache

<table>
<thead>
<tr>
<th>EVG/Cobi/TDF/FTC</th>
<th>AM</th>
<th>PM</th>
</tr>
</thead>
<tbody>
<tr>
<td>take 1 tablets orally daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>with food</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

EVG/Cobi/TAF/FTC

take 1 tablets orally daily
with or without food

Dolutegravir

- Common AEs: insomnia, headache, rash
- Metabolized by UGT1A1 and CYP3A (10-15%)
- Only use w/ETR if w/ATV/r, DRV/r, or LPV/r

<table>
<thead>
<tr>
<th>Adult Population</th>
<th>Dose</th>
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<tr>
<td>Tx-naïve or -experienced, INSTI-naive</td>
<td>30 mg QD</td>
</tr>
<tr>
<td>Tx-naïve or -experienced, INSTI-naive; when w/ fos-APV/r or TPV/r or potent UGT1A/CYP3A inducers</td>
<td>30 mg BID</td>
</tr>
<tr>
<td>INSTI-experienced with certain INSTI resistance or clinically suspected INSTI resistance</td>
<td>50 mg BID</td>
</tr>
</tbody>
</table>

- Dolutegravir, DLG

take 1 tablets (50mg) orally daily
with or without food

DTG & Kidneys

- DTG inhibits renal organic cation transporters (OCT) & multidrug and toxin extrusion (MATE) transporter
- inhibits tubular secretion of creatinine by inhibiting OCT & MATE
- \( \uparrow \) Scr within 1st 4 weeks of treatment; mean change from baseline = 0.15 mg/dL (10-14% decrease CrCl)
- DTG may \( \uparrow \) plasma concentrations of drugs eliminated via OCT or MATE (e.g., metformin)

Dolutegravir

- Common AEs: insomnia, headache, rash
- Metabolized by UGT1A1 and CYP3A (10-15%)
- Only use w/ETR if w/ATV/r, DRV/r, or LPV/r

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<tr>
<td>INSTI-experienced with certain INSTI resistance or clinically suspected INSTI resistance</td>
<td>50 mg BID</td>
</tr>
</tbody>
</table>

- Dolutegravir, DLG

take 1 tablets (50mg) orally daily
with food

DTG & Kidneys

- In severe renal impairment, DTG plasma concentrations \( \downarrow \)
  (~40% \( \downarrow \) AUC vs. normal renal function)
- Possible explanation: reduction in absorption
  - Severe renal impairment may alter GI transit time or result in bacterial overgrowth in GIT that may affect drug absorption
  - Do not need to dose adjust DTG in those with renal impairment (CrCl \( < 30 \) mL/min, not on HD)

DTG & Hemodialysis

- DTG QD added to participants’ stable ART regimen x5 days
- On day 5, blood samples at beginning & end of HD session, samples of blood entering & leaving dialyzer, & resulting dialysate collected 1 hr after start of HD session for DTG levels
- **Results:**
  - Median HD extraction ratio = 7%, w/ negligible DTG in dialysate
  - Minimal DTG removal by HD, no dosage adjustments required
- **Conclusion:** no DTG dose adjustment necessary in HD b/c of minimal extraction ratio of DTG by HD & DTG plasma concentrations far above protein-binding-adjusted IC90


DTG PK Post-EFV

- **DTG:** metabolized by UGT1A1 & minor substrate of CYP3A4
- **EFV:**
  - CYP3A4 & UGT1A1 inducer
  - ↓ DTG AUC by 57% & Ctrough by 75%
  - Need BID DTG when w/EFV
- **PK sub-study of STRIVING:**
  - N=24 on EFV-based regimen
  - Blood samples prior to DTG dose on day 1, then weeks 1, 2, 4, 8, & 24

(de W et J, et al. 17th International Workshop on Clinical Pharmacology of HIV & Hepatitis Therapy. 2016; Washington, DC)

DTG PK Post-EFV

- All 24 participants maintained VL<50 until week 24
- Alter switch to ABC/3TC/DTG, DTG concentrations above IC90 at all times
- PK & virologic data support switch w/o need for 1-2 weeks DTG dose increase

Question #5: Which cations can be taken together with DTG if taking them with food?

1. Calcium and Magnesium
2. Calcium and Iron
3. Magnesium and Iron
4. Magnesium and Aluminum
Cations + DTG

- Due to chelation, metal cations significantly ↓ DTG
- Open-label study in healthy volunteers, randomized to DTG 50mg + calcium carbonate 1200mg or DTG + ferrous fumarate 324mg

- Ca + DTG w/o meals ↓ DTG exposure by 1/3
- Fe + DTG w/o meals ↓ DTG exposure by 1/2


Question #6: Which of the following is correct?

1. RAL is NOT recommended to be co-administered or staggered w/ Al or Mg-antacids
2. There is no dose adjustment necessary when RAL is co-administered with Ca carbonate antacids
3. Separate EVG and antacids containing Ca, Mg, or Al by at least 2 hours
4. Administer DTG 2 hours before or 6 hours after Mg, Al, Ca, or Fe
5. All of the above are correct

Summary: Integrase Inhibitors

- DTG, EVG/c, & RAL are part of ARV preferred regimens
- Generally well-tolerated
- EVG/c has many drug-drug interactions due to inhibition of many enzymes (e.g., CYP3A, P-gp, …)
- Other unexpected interactions:
  - DTG + metformin
  - DTG + ETR
  - INSTI + polyvalent cations
  - DTG and EVG/c decrease CrCl without affecting GFR
- Need to monitor Scr

Protease Inhibitors

**Darunavir**

- No DRV-specific mutations: 800mg DRV+100mg RTV QD
- Or cobicistat 150mg QD in a FDC
- ≥1 DRV-specific mutations: 600mg DRV+100mg RTV BID
- Precaution: sulfa moiety
  - fos-amprenavir, darunavir, & tipranavir

<table>
<thead>
<tr>
<th>Darunavir, DRV</th>
<th>AM</th>
<th>PM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Take 1 tablet (800mg) usually once daily with ritonavir if needed</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ritonavir, RTV</th>
<th>AM</th>
<th>PM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Take 1 tablet (100mg) usually once daily</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**DRV & TMP-SMX Cross-reactivity**

- DRV & TMP-SMX contain sulfonamide moiety (SO2NH2)
- Incidence of allergic cutaneous reactions to TMP-SMX in HIV+ patients= 21.5-39%
- DRV registration trials reported HSR ~16%
- 2 studies in HIV+ Asian patients, found no association between DRV/r rash & TMP-SMX allergy


**Question #7: If a patient has a sulfa allergy, can I use DRV?**

1. Yeah, it’s totally fine
2. I’m not sure, let me check with my clinical pharmacist
**( DRV & TMP-SMX Cross-reactivity)**

- Retrospective cohort study in 2 hospitals in the Netherlands
- N=79 history of TMP-SMX allergy
- DRV allergy seen in 4 (5.1%) w/ TMP-SMX allergy vs. 4 (1.2%) w/o TMP-SMX allergy (p=0.05)
- Patients with TMP-SMX allergy at ↑ risk for DRV allergy (OR=4.3)
- No potentially lethal allergic reactions
- **Bottom line:** Probably safe to administer DRV in patients allergic to TMP-SMX as long as allergy not life-threatening.

Bianca, B.S., et al. AIDS. 2015

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**Summary:** Protease Inhibitors

- DRV/r is the only PI in the list of preferred ARV regimens
- There are many drug-drug interactions with PI/r due to CYP450 inhibition
- DRV/r is generally well-tolerated but the PI class has many GI, metabolic, & CV adverse effects associated with it

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**PI-Oral Contraceptive Interaction**

<table>
<thead>
<tr>
<th></th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atazanavir/r</td>
<td>≥35 mcg EE</td>
</tr>
<tr>
<td>Atazanavir</td>
<td>≤30 mcg EE</td>
</tr>
<tr>
<td>Darunavir/r</td>
<td>Use alternative methods</td>
</tr>
<tr>
<td>Fos-amprenavir/r</td>
<td>Use alternative methods</td>
</tr>
<tr>
<td>Lopinavir/r</td>
<td>Use alternative methods</td>
</tr>
</tbody>
</table>

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**Reminder: Case #1**

You would like to start ARVs for your 45 y/o White HIV+ female patient. She would like a once-daily regimen. She has normal liver and kidney function. She has no ARV drug resistance at baseline and has never taken ARVs.

**Labs:**
- VL=178K copies/mL
- CD4+=458 cells/mm³
- HLA-B5701+

**Meds:**
- ethinyl estradiol/norethindrone
- metformin
- calcium/vitamin D

**Allergies:** sulfa (mild rash)
Case #2

Your patient is a 52 y/o African American male with PMH of HIV, hyperlipidemia, and seasonal allergies. He is taking atorvastatin (10mg QD) and using beclomethasone nasal spray. He has not been willing to start ARVs but feels that he’s ready now if we can give him a once-daily regimen.

- Labs:
  - HLA-B*5701: negative
  - Genotype: K103N (resistance to EFV)
  - CrCl: 60 mL/min

<table>
<thead>
<tr>
<th>Date</th>
<th>CD4 (ABS)</th>
<th>HIV Viral Load</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/11/2015</td>
<td>665</td>
<td>10,171</td>
</tr>
<tr>
<td>6/18/2015</td>
<td>849</td>
<td>11,096</td>
</tr>
<tr>
<td>11/19/2015</td>
<td>697</td>
<td>12,506</td>
</tr>
<tr>
<td>3/29/2016</td>
<td>625</td>
<td>387</td>
</tr>
<tr>
<td>8/18/2016</td>
<td>530</td>
<td>33</td>
</tr>
</tbody>
</table>

- Cholesterol
  - HDL: 42
  - LDL-CALC: 183 (H)
Factors to consider for Case #2...

- Drug resistance testing: K103N (resistance to EFV)
- History of ARV use & prior drug resistance tests: none
- Comorbidities: hyperlipidemia & allergies
- Drug adverse effects & allergies: no known
- Drug-drug interactions: atorvastatin & beclo nasal spray
- Pregnancy: N/A
- Labs: HLA-B5701-, CD4+=530, VL=12K, LDL=180, TG=138, CrCl=60, normal liver function
- Factors potentially influencing adherence: QD regimen

Case #2: Drug-drug Interactions

1. Atorvastatin (10mg QD)
2. Beclomethasone nasal spray

ARV-Statin Drug-Drug Interactions

<table>
<thead>
<tr>
<th>Statin</th>
<th>ARV</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrova</td>
<td>ATV/r</td>
<td>Use lowest dose and titrate slowly</td>
</tr>
<tr>
<td></td>
<td>DRV/r, fos-APV/r</td>
<td>Use lowest dose and titrate slowly (Do not exceed 20mg?)</td>
</tr>
<tr>
<td></td>
<td>LPV/r</td>
<td>Use lowest dose &amp; w/caution</td>
</tr>
<tr>
<td></td>
<td>EVG/COBI</td>
<td>Use lowest dose and titrate slowly</td>
</tr>
<tr>
<td>Pitava</td>
<td>All PIs</td>
<td>No dose adjustment needed</td>
</tr>
<tr>
<td></td>
<td>EVG/COBI</td>
<td>No dosage recommendation</td>
</tr>
<tr>
<td>Pravas</td>
<td>DRV/r</td>
<td>Use lowest dose and titrate slowly</td>
</tr>
<tr>
<td></td>
<td>EVG/COBI</td>
<td>No dosage recommendation</td>
</tr>
<tr>
<td>Rosuva</td>
<td>ATV/r, LPV/r</td>
<td>Use lowest dose and titrate slowly (Do not exceed 10mg)</td>
</tr>
<tr>
<td></td>
<td>DRV/r, EVG/COBI</td>
<td>Use lowest dose and titrate slowly</td>
</tr>
</tbody>
</table>

Lova- & Simva-: contraindicated with PIs & EVG/COBI

Inhaled Corticosteroids

- Cushing’s syndrome: central obesity, weight gain, dorsocervical fat pad, easy bruising, facial plethora, rapid weight gain, increased appetite, facial hirsutism
- Do not co-administer fluticasone w/ RTV or PIs (or COBI)
- Case reports w/ mometasone and budesonide
- Beclomethasone is a relatively safe option with PIs
- Based on PK, flunisolide appears to have a low risk of drug-drug interactions

### Recommended Regimens

<table>
<thead>
<tr>
<th></th>
<th>ABC/3TC**</th>
<th>TDF/FTC or TAF/FTC*</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF/FTC</td>
<td>ABC/3TC</td>
<td>TDF/FTC or TAF/FTC*</td>
</tr>
<tr>
<td>TDF/FTC</td>
<td>ABC/3TC</td>
<td>TDF/FTC or TAF/FTC*</td>
</tr>
</tbody>
</table>

* TDF/FTC not recommended if CrCl <70 & TAF/FTC not recommended if CrCl <30
** If HLA-B*5701 is negative
*** If pre-treatment HIV RNA <100,000 copies/mL & CD4 >200 cells/mm³

http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf

### Drug Information Resources

- **Drug resistance**
  - HIV Drug Resistance Testing Database: hivdb.stanford.edu/
- **Drug-drug interactions**
  - Package inserts
- **Toronto General HIV Clinic**: www.hivclinic.ca
- University of Liverpool: www.hiv-druginteractions.org/
- Pubmed
- HIV InSite: hivinsite.ucsf.edu/InSite
- NATAP: natap.org

- **Dosage modifications**
  - NCCC chart: nccc.ucsf.edu
  - Micromedex
  - Package inserts

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