Disclosures

- Speaker
  - AbbVie, BMS, Gilead, Janssen, Merck
- Consultant
  - BMS, Gilead, ViiV
Northeast/Caribbean AETC

- Funded by HRSA
- Multiple Regions across United States
- Focus on training, practice transformation, as it relates to HIV and HCV care
- Our region covers – NY, NJ, PR, USVI
Rates of Adults and Adolescents Living with Diagnosed HIV Infection, Year-end 2013—United States and 6 Dependent Areas

N = 950,811 Total Rate = 355.9

Note. Data include persons with a diagnosis of HIV infection regardless of stage of disease at diagnosis. All displayed data have been statistically adjusted to account for reporting delays, but not for incomplete reporting.
Estimating the Lifetime Risk of HIV Diagnosis in the U.S. National HIV Surveillance System Census Data

Mortality Data from National Center for Health Statistics (2009-2013, US census data)

Methods:
- HIV diagnoses and non-HIV deaths used to calculate the probability of HIV diagnosis at a given age
- Lifetime risk = cumulative probability of HIV diagnosis from birth (results presented as 1 in N)

Results: Lifetime Risk of Acquiring HIV
- Overall in USA: 1 in 99
- Black MSM: 1 in 2
- Hispanic MSM: 1 in 4
- White MSM: 1 in 11
Kaiser Life Expectancy Cohort

- Kaiser cohort data from 1996-2011 evaluating life expectancy between HIV+ (n=25,768; 46% on ART at BL) and HIV- (n=257,600) subjects
- **Mortality rate of 1,827 vs. 326 per 100,000 person-years, respectively**
- Abridged life tables were used to estimate years of life remaining at age 20

### Expected years of life remaining at age 20 (95% confidence interval)

<table>
<thead>
<tr>
<th></th>
<th>HIV+</th>
<th>HIV-</th>
<th>Difference</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>49.3</td>
<td>62.3</td>
<td><strong>13.1 (11.5-14.6)</strong></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HIV+ and initiated ART with CD4 500</td>
<td>54.5</td>
<td>62.3</td>
<td><strong>7.9 (5.1-10.6)</strong></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>+ No hepatitis B or C</td>
<td>55.4</td>
<td>62.6</td>
<td><strong>7.2 (4.4-10.0)</strong></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>+ No drug/alcohol abuse</td>
<td>57.2</td>
<td>63.8</td>
<td><strong>6.6 (3.9-9.3)</strong></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>+ No smoking</td>
<td>58.9</td>
<td>64.3</td>
<td><strong>5.4 (2.2-8.7)</strong></td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Even with early ART initiation, a life expectancy gap remains between HIV+ and HIV- subjects.

Mitigation of risk factors, like smoking, may further reduce the survival disparity.
Challenges in Linkage to Care and Successful Treatment

Estimated that only 19% of HIV-infected individuals in the US have undetectable HIV viral load.
DHHS Guidelines, When to Start
Immediate Versus Deferred ART: START

HIV-positive (N = 4685) Adults
Treatment-naive CD4 cell count >500 cells/mm³

Immediate ART
ART initiated immediately following randomization
(n = 2326)

Deferred ART
Deferred until CD4+ cell count ≤ 350 cells/mm³, AIDS, or event requiring ART
(n = 2359)

- Primary endpoint: Composite outcome of 2 major components
  - Any serious AIDS-related event
  - Any serious non-AIDS-related event

START, Strategic Timing of AntiRetroviral Treatment.
Primary outcome

- **57% Reduced Risk of Serious Events or Death With Immediate ART**
- **4.1% vs 1.8% in deferred vs immediate arms experienced serious AIDS or non-AIDS–related event or death** (HR: 0.43; 95% CI: 0.30-0.62; P < .001)
- Study stopped early (May 2015) - Median time until initiation of ART in the deferred ART group: 3 years

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Community Viral Load Mirrors Reduced Rate of New HIV Cases in San Francisco

- Retrospective analysis of relationship between community viral load (CVL; mean of summed individual HIV-1 RNA results per yr) and new HIV diagnoses

![Graph showing mean CVL and number of newly diagnosed HIV cases over years 2004 to 2008.]

- Mean CVL:
  - 2004: 798
  - 2005: 642
  - 2006: 523
  - 2007: 518
  - 2008: 434

- Number of newly diagnosed HIV cases:
  - 2004: 798
  - 2005: 642
  - 2006: 523
  - 2007: 518
  - 2008: 434

*Data insufficient to prove significant association with reduced HIV incidence.

ART is recommended for all HIV-infected individuals to reduce the risk of disease progression.\textsuperscript{a}

ART is also recommended for HIV-infected individuals to diminish the risk of HIV transmission.\textsuperscript{b}

Patients starting ART should be willing and able to commit to treatment and understand the benefits and risks of therapy and the importance of adherence.

Patients may choose to postpone therapy, and providers, on a case-by-case basis, may elect to defer therapy on the basis of clinical and/or psychosocial factors.
DHHS Guidelines, What to Start
## Available Antiretroviral Medications (2016)

<table>
<thead>
<tr>
<th>NRTIs</th>
<th>PIs</th>
<th>INSTIs</th>
<th>Fusion Inhibitor</th>
<th>CCR5 Inhibitor</th>
<th>PKE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir (ABC)</td>
<td>Atazanavir (ATV)</td>
<td>Dolutegravir (DTG)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Didanosine (ddI)</td>
<td>Darunavir (DRV)</td>
<td>Elvitegravir (EVG)</td>
<td></td>
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</tr>
<tr>
<td>Emtricitabine (FTC)</td>
<td>Fosamprenavir (FPV)</td>
<td>Raltegravir (RAL)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Lamivudine (3TC)</td>
<td>Indinavir (IDV)</td>
<td></td>
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</tr>
<tr>
<td>Stavudine (d4T)</td>
<td>Lopinavir (LPV)</td>
<td></td>
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</tr>
<tr>
<td>Tenofovir alafenamide</td>
<td>Nelfinavir (NFV)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Tenofovir (TDF)</td>
<td>Ritonavir (RTV)</td>
<td></td>
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</tr>
<tr>
<td>Zidovudine (AZT, ZDV)</td>
<td>Saquinavir (SQV)</td>
<td></td>
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</tr>
<tr>
<td><strong>NNRTIs</strong></td>
<td>Tipranavir (TPV)</td>
<td></td>
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<tr>
<td>Delavirdine (DLV)</td>
<td></td>
<td>Enfuvirtide (ENF, T-20)</td>
<td></td>
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<td></td>
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<tr>
<td>Efavirenz (EFV)</td>
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<tr>
<td>Etravirine (ETR)</td>
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<tr>
<td>Nevirapine (NVP)</td>
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<tr>
<td>Rilpivirine (RPV)</td>
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</tr>
</tbody>
</table>

CCR5, C-C chemokine receptor type 5; INSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; PKE, pharmacokinetic enhancer.

Initial Treatment: Choosing Regimens

- 3 main categories:
  - 1 NNRTI + 2 NRTIs
  - 1 PI + 2 NRTIs
  - 1 II + 2 NRTIs

Combination of PI (DRV/r), or II + 2 NRTIs preferred for most patients

- Fusion inhibitor, CCR5 antagonist not recommended in initial ART
- Few clinical end points to guide choices
- Advantages and disadvantages to each type of regimen
- Individualize regimen choice

www.aidsetc.org
What Regimen to Start, DHHS Recommended Regimens, July 2016

- **Integrase Strand Transfer Inhibitor-Based Regimens:**
  - Dolutegravir/abacavir/lamivudine—only for patients who are HLA-B*5701 negative (AI)
  - Dolutegravir plus either tenofovir disoproxil fumarate/emtricitabine (AI) or tenofovir alafenamide/emtricitabine (AII)
  - Elvitegravir/cobicistat/tenofovir alafenamide/emtricitabine (AI)
  - Elvitegravir/cobicistat/tenofovir disoproxil fumarate/emtricitabine (AI)
  - Raltegravir plus either tenofovir disoproxil fumarate/emtricitabine (AI) or tenofovir alafenamide/emtricitabine (AII)

- **Protease Inhibitor-Based Regimens:**
  - Darunavir/ritonavir plus either tenofovir disoproxil fumarate/emtricitabine (AI) or tenofovir alafenamide/emtricitabine (AII)
**DHHS July 2016, Recommended Regimens**

<table>
<thead>
<tr>
<th>PI – Based Regimens:</th>
<th>Brand Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darunavir/ritonavir + TDF/FTC or TAF/FTC</td>
<td>Prezista/Norvir Truvada (AI) Prezista/Norvir Descovy (AII)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>INSTI – Based Regimens:</th>
<th>Brand Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dolutegravir/abacavir/lamivudine – ONLY if patient HLA-B*5701 negative</td>
<td>Triumeq (AI)</td>
</tr>
<tr>
<td>Dolutegravir + TDF/FTC or TAF/FTC</td>
<td>Tivicay Truvada (AI) Tivicay Descovy (AII)</td>
</tr>
<tr>
<td>Elvitegravir/cobicistat/TDF/FTC</td>
<td>Stribild (AI)</td>
</tr>
<tr>
<td>Elvitegravir/cobicistat/TAF/FTC</td>
<td>Genvoya (AII)</td>
</tr>
<tr>
<td>Raltegravir + TDF/FTC or TAF/FTC</td>
<td>Isentress Truvada (AI) Isentress Descovy (AII)</td>
</tr>
</tbody>
</table>

TDF=tenofovir disoproxil fumarate, TAF=tenofovir alafenamide, FTC=emtricitabine
TAF – In Descovy, Odefsey, Genvoya

Tenofovir Alafenamide

- Tenofovir Alafenamide 25mg Pharmacokinetics
  - 4-7 fold higher TFVdp in PBMCS than TDF 300mg
  - 7 fold lower TFV in plasma than TDF 300mg

- Mucosal tissue concentrations unknown

Adapted from Liu Y. Poster Number H-664, ICAAC 2013.
Tivicay + Truvada or Descovy OR Triumeq

Key Points

- Adverse events > 2% were insomnia and headache
- Renal and bone side effects possible with tenofovir DF, TAF less likely
- Hypersensitivity reaction associated with abacavir; HLAB701 screening prior to starting, if using Triumeq
  - Flu like illness
  - Rash, fever constitutional symptoms
  - HLA B5701 association
Stribild Key Points

- One pill once daily – complete regimen in one tablet
- GI side effects from cobicistat
- Increased serum creatinine from blocking tubular secretion
- Renal and bone side effects possible with tenofovir DF
- Drug Drug Interactions for cobicistat similar to RTV
Genvoya Key Points

- One pill once daily – complete regimen in one tablet
- GI side effects from cobicistat
- Increased serum creatinine from blocking tubular secretion
- TAF replaces TDF in Genvoya
  - Less proteinuria, better bone profile
- Drug Drug Interactions for cobicistat similar to RTV
Isentress + Truvada or Descovy Key Points

- 3 tablets
- Isentress dosed twice a day
  - Once daily dosing possible, but inferior to BID
- Well tolerated, no effect on lipids
- Renal side effects possible with tenofovir DF, less if using TAF
Prezista Norvir + Truvada or Descovy

Key Points

- 3 tablets daily
- “Boosted” PI regimen
- Dosed once a day with food
- GI side effects, minimal effect on lipids
- Sulfa moiety
- Renal side effects possible with tenofovir DF, less likely with TAF
- DRV/c/TAF/FTC in development
Norvir or Cobicistat Boosted Protease Inhibitors

- Less resistance – nearly no resistance reported in naïve trials with all boosted PI regimens currently on guidelines
- Boosted Integrase inhibitors, not the same, resistance can happen in naives– ie Genvoya, Stribild
- Lower pill burdens
- Reduced frequency – now all are once daily, versus 2-3 times daily for unboosted protease inhibitors
- “Ritonaphobia” is the REAL downside
DHHS Guidelines Initial Recommended Regimens - 2016

Tivicay + Truvada or Descovy OR Triumeq

OR

1-2/day

Stribild OR Genvoya

1/day

DHHS Guidelines Initial Recommended Regimens - 2016

Prezista Norvir Truvada or Descovy

Isentress (BID) Truvada

3/day
Pill Burden, STRs to Scale

Pills displayed are actual size and do not contain any medicine.
3-Drug Combination ART 1996: Crixivan/Retrovir/Epivir

- **SAM**
- **4PM**
- **12 MID**

Fasting (1 hour before/2 hours after) meals. 1.5 liters of hydration/day.
Daily Pill Box – 2002
MEGA HAART
Kaletra/Fortovase/Sustiva/Viread/Videx/Epivir – 23 pills!!

"I trust the meal meets with Sir's approval?"
# DHHS July 2016, Alternative Regimens

## PI – Based Regimens:

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>PI – Based Regimens:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evotaz or Reyataz/Norvir+</td>
<td>Atazanavir/cobicistat OR Atazanavir/ritonavir+ TDF/FTC OR TAF/FTC</td>
</tr>
<tr>
<td>Truvada (BII) or Descovy (BII)</td>
<td></td>
</tr>
<tr>
<td>Prezcobix + Truvada (BII) or Descovy (BII)</td>
<td>Darunavir/cobicistat + TDF/FTC or TAF/FTC</td>
</tr>
<tr>
<td>Prezcobix + Epzicom (BIII) Prezista/Norvir + Epzicom (BII)</td>
<td>Darunavir/cobicistat OR Darunavir + ritonavir + abacavir/lamivudine ONLY if HLA-B*5701 negative</td>
</tr>
</tbody>
</table>

## NNRTI – Based Regimens:

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>NNRTI – Based Regimens:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atripla (BII) or Sustiva + Descovy (BII)</td>
<td>Efavirenz/TDF/FTC OR Efavirenz + TAF/FTC</td>
</tr>
<tr>
<td>Complera (BII) or Odefsey (BII)</td>
<td>Rilpivirine/TDF/FTC or Rilpivirine/TAF/FTC ONLY if pretreatment VL&lt;100,000 copies/ml and CD4 &gt;200 cells/mm³</td>
</tr>
</tbody>
</table>

TDF=tenofovir disoproxil fumarate, TAF=tenofovir alafenamide, FTC=emtricitabine
Atripla Key Points

- 3 drugs in one tablet
- Efavirenz/tenofovir DF/emtricitabine
- AKA Sustiva+Truvada
- Dosed at bedtime usually
- Pregnancy Category D
- CNS side effects common in first few weeks
- Renal side effects possible with tenofovir
Complera Key Points

- One pill once daily – complete regimen in one tablet
- **ONLY if** pretreatment VL < 100,000 copies/ml and CD4 > 200 cells/mm³
- Contains TDF
- QT prolongation possible with rilpivirine
- Contraindicated with Proton Pump Inhibitors
Odefsey Key Points

- One pill once daily – complete regimen in one tablet
- ONLY if pretreatment VL<100,000 copies/ml and CD4 >200 cells/mm³
- Contains TAF, only difference between Odefsey and Complera
  - Less proteinuria, better bone profile
- QT prolongation possible with rilpivirine
- Contraindicated with Proton Pump Inhibitors
DHHS Guidelines, What NOT to Use
ARVs Not Recommended in Initial Treatment

<table>
<thead>
<tr>
<th>Virologic failure</th>
<th>Didanosine + Tenofovir DF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inferior virologic efficacy</td>
<td>ABC + 3TC + ZDV as 3-NRTI regimen</td>
</tr>
<tr>
<td></td>
<td>ABC + 3TC + ZDV + TDF as 4-NRTI regimen</td>
</tr>
<tr>
<td></td>
<td>Didanosine + (lamivudine OR emtricitabine)</td>
</tr>
<tr>
<td></td>
<td>Unboosted Atazanavir, Fosamprenavir, Saquinavir</td>
</tr>
<tr>
<td></td>
<td>Delavirdine</td>
</tr>
<tr>
<td></td>
<td>Nelfinavir</td>
</tr>
<tr>
<td></td>
<td>Tipranavir/ritonavir</td>
</tr>
<tr>
<td>High incidence of toxicities</td>
<td>Zidovudine + lamivudine</td>
</tr>
<tr>
<td></td>
<td>Stavudine + lamivudine</td>
</tr>
<tr>
<td></td>
<td>Didanosine + tenofovir DF</td>
</tr>
<tr>
<td></td>
<td>Nevirapine</td>
</tr>
<tr>
<td></td>
<td>Indinavir/ritonavir</td>
</tr>
<tr>
<td></td>
<td>Ritonavir as sole PI</td>
</tr>
</tbody>
</table>
## ARVs Not Recommended in Initial Treatment (2)

<table>
<thead>
<tr>
<th>Potential for drug-drug interactions</th>
<th>EVG/COBI/TDF/FTC + other ARV drugs</th>
</tr>
</thead>
</table>
| High pill burden/ dosing inconvenience | Indinavir (unboosted)  
Saquinavir/ritonavir |
| Lack of data in initial treatment | Abacavir + Didanosine  
Fosamprenavir/ritonavir  
Darunavir (unboosted)  
Enfuvirtide (T-20)  
Etravirine |
| No benefit over standard regimens | 3-class regimens  
3 NRTIs + NNRTI  
Maraviroc |
ARV Medications: Should Not Be Offered at Any Time

- ARV regimens not recommended:
  - Monotherapy with NRTI*
  - Monotherapy with boosted PI
  - Dual-NRTI therapy
  - 3-NRTI regimen (except ABC + 3TC + ZDV or possibly TDF + 3TC + ZDV)

* ZDV monotherapy is not recommended for prevention of perinatal HIV transmission but might be considered in certain circumstances; see Public Health Service Task Force Recommendations for the Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States.
ARV Medications: Should Not Be Offered at Any Time (2)

- ARV components not recommended:
  - Didanosine + Stavudine
  - Didanosine + Tenofovir DF
  - Emtricitabine + Lamivudine
  - Stavudine + Zidovudine
  - Darunavir, Saquinavir, or Tipranavir as single PIs
  - Atazanavir + Indinavir
ARV Medications: Should Not Be Offered at Any Time (3)

- ARV components not recommended:
  - EFV during first trimester of pregnancy and in women with significant potential for pregnancy*
  - NVP initiation in women with CD4 counts of >250 cells/µL or in men with CD4 counts of >400 cells/µL
  - ETR + unboosted PI
  - ETR + RTV-boosted ATV, FPV, or TPV
  - 2-NNRTI combination

* Exception: when no other ARV options are available and potential benefits outweigh the risks
Pre-exposure Prophylaxis
PrEP
PrEP

- Fixed dose combination of tenofovir disoproxil fumarate (TDF) 300mg and emtricitabine (FTC) 200mg. Brand name: Truvada
- Only antiretroviral drug approved by FDA for this purpose
- Taken orally, one pill daily
## Overall Results of PrEP Trials, CDC

<table>
<thead>
<tr>
<th>Clinical trial</th>
<th>Participants</th>
<th>Type of medication</th>
<th>mITT efficacy*</th>
<th>Adherence-adjusted efficacy based on TDF detection in blood</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>%</td>
</tr>
<tr>
<td>Bangkok Tenofovir Study</td>
<td>Injecting drug users</td>
<td>TDF</td>
<td>49</td>
<td>(10–72)</td>
</tr>
<tr>
<td>Partners PreEP</td>
<td>HIV discordant couples</td>
<td>TDF</td>
<td>67</td>
<td>(44–81)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TDF/FTC</td>
<td>75</td>
<td>(55–87)</td>
</tr>
<tr>
<td>TDF2</td>
<td>Heterosexually active men and women</td>
<td>TDF/FTC</td>
<td>62</td>
<td>(22–83)</td>
</tr>
<tr>
<td>iPrEx</td>
<td>Men who have sex with men</td>
<td>TDF/FTC</td>
<td>42</td>
<td>(18–60)</td>
</tr>
<tr>
<td>Fem-PrEP</td>
<td>Heterosexually active women</td>
<td>TDF/FTC</td>
<td>NS</td>
<td>—</td>
</tr>
<tr>
<td>VOICE</td>
<td>Heterosexually active women</td>
<td>TDF</td>
<td>NS</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TDF/FTC</td>
<td>NS</td>
<td>—</td>
</tr>
</tbody>
</table>

2014 CDC PrEP Guidelines

- PrEP Guidelines released in May 2014
- Addresses the role of tenofovir/emtricitabine in the following adult populations
  - Men who have sex with men
  - Heterosexual men and woman
  - Injection Drug Users
  - Sero-discordant couples

TAF - PBMC good, other tissues...
Vaginal Ring

BULLETIN
NIAID to Fund Further Study of Dapivirine Vaginal Ring for HIV Prevention
Investment in HOPE Trial Augments Development of Next-Generation Prevention Tools
March 13, 2016

The National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH), announced today that it would move forward with an open-label extension study of an HIV prevention tool for women: a silicone ring that continuously releases the experimental antiretroviral drug dapivirine in the vagina. The new study builds on recently announced findings from the ASPIRE trial which found that the dapivirine ring safely provided a modest level of protection against HIV infection in sub-Saharan African women. The dapivirine ring reduced the risk of HIV infection by 27 percent in the study population overall and by 61 percent among women ages 25 years and older, but provided no statistically significant protection in women younger than 25 years. This product is one of several HIV prevention.
CAB – Injectable PrEP

Predicted and Observed Mean (SD) CAB Concentration

- Geometric mean $C_T$: 10 mg PO QD
  - LATTE, 1.35 μg/mL
- $4 \times PA-IC_{90}$: 0.664 μg/mL
- $PA-IC_{90}$: 0.166 μg/mL

Plasma CAB (μg/mL)

- Simulated CAB 800 mg IM Q12W (males)

Time from IM Dose 1 (weeks)

$C_T$, concentration at the end of the dosing interval; $PA-IC_{90}$, protein binding–adjusted 90% inhibitory concentration; SD, standard deviation.
Summary: Prescribing PrEP

- Daily FTC/TDF shown to have moderate efficacy for HIV-1 prevention among MSM
  - High efficacy among those with high adherence
  - PrEP is a promising HIV prevention strategy for MSM
- Daily TDF and FTC/TDF safe and efficacious among heterosexual couples and young heterosexuals
- Providers should be prepared to do risk assessment, counseling, and prescribe for high-risk MSM
Post Exposure Prophylaxis
Preferred HIV PEP Regimen – 28 Days

Raltegravir (Isentress; RAL) 400 mg PO twice daily

PLUS

Truvada, 1 PO once daily
(Tenofovir DF [Viread; TDF] 300 mg + emtricitabine [Emtriva; FTC] 200 mg) Fixed Dose Combination
Drug Interaction Prevention
Basics of Drug Elimination
Pharmacokinetic Interactions

- Most common type of interactions in HIV
  - Absorption – reduced atazanavir absorption when combined with proton pump inhibitors
  - Distribution – protein binding displacement when warfarin and SMZ/TMP are combined
  - **Metabolism** – elevated simvastatin levels when ritonavir inhibits CYP450 enzyme
  - Elimination – competition for renal elimination with probenicid and penicillin
- Also other transporters such as PGP, OAT, etc
CYP450 Metabolism for FDA Approved Medications

Key points
• Majority of drugs metabolized by CYP3A4 & CYP2D6
• CYP3A4 involved with HIV PI/NNRTI/cobicistat, also HCV PI metabolism
• Enzymes can be induced or inhibited
Key Points

- Adding a CYP3A4 INDUCER leads to DECREASED levels of the other medication that is also metabolized by CYP3A4.
- Peak effect of inducer occurs SLOWLY based upon half-life of drug & time to synthesize new CYP3A4 enzyme.
- Example - Adding efavirenz to a methadone or to a PI.
Select CYP3A4 Inducers

- Carbamazepine
- Efavirenz
- Fosphenyton
- Nevirapine
- St. John’s Wort
- Oxcarbazepine
- Phenobarbital
- Phenytoin
- Rifabutin
- Rifampin
CYP450 Inhibition

Key Points
- Adding a CYP3A4 INHIBITOR leads to INCREASED levels of the other medication that is also metabolized by CYP3A4.
- Peak effect occurs RAPIDLY, as soon as adequate concentrations of the CYP3A4 inhibitor being added are reached.
- Classic example - Adding Darunavir/rtv or cobicistat to simvastatin.

Steady State Levels

Drug Levels

Inhibiting drug added

Time
Common CYP3A4 Inhibitors

- Clarithromycin
- Cobicistat
- Delavirdine
- Erythromycin
- Fluconazole

- HCV Protease Inhibitors
- HIV Protease Inhibitors
- Itraconazole
- Ritonavir
Boosters – Ritonavir

- Ritonavir
  - Most major interactions worked out
  - Anything in a new drug label that mentions strong CYP3A4 inhibitors, think ritonavir
  - Also inhibits PGP, CYP2D6, OAT transporters
Boosters – Cobicistat

- Co-formulated with elvitegravir, cobicistat, tenofovir DF (and TAF) and emtricitabine
- Contraindicated medications almost identical to ritonavir
- Anything you would use with caution in the PI class should be used with caution with cobicistat
- Mostly a CYP3A4 inhibitor, minor 2D6, minimal if any PGP interactions
Contraindicated Medications with Protease Inhibitors

- Alfuzosin
- Cisapride
- Colchicine
- Dronedarone
- Ergotamine derivatives
- Lovastatin, simvastatin
- Lurasidone
- Oral midazolam and triazolam
- Pimozide
- Ranolazine
- Rifampin
- Sildenafil for pulmonary arterial hypertension
- St. John’s Wort
Contraindicated Meds, Cobicistat

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Drug name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha 1-adrenoreceptor antagonist</td>
<td>Alfuzosin</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Carbamazepine, phenobarbital, phenytoin</td>
</tr>
<tr>
<td>Antimycobacterial</td>
<td>Rifampin</td>
</tr>
<tr>
<td>Ergot derivatives</td>
<td>Dihydroergotamine, ergotamine, methylergonovine</td>
</tr>
<tr>
<td>GI motility agent</td>
<td>Cisapride</td>
</tr>
<tr>
<td>Herbal products</td>
<td>St. John’s wort</td>
</tr>
<tr>
<td>HMG-CoA reductase inhibitors</td>
<td>Lovastatin, simvastatin</td>
</tr>
<tr>
<td>Neuroleptic</td>
<td>Pimozide</td>
</tr>
<tr>
<td>PDE-5 inhibitor</td>
<td>Sildenafil when dosed as Revatio® for the treatment of pulmonary arterial hypertension</td>
</tr>
<tr>
<td>Sedative/hypnotics</td>
<td>Triazolam, orally administered midazolam</td>
</tr>
</tbody>
</table>

DHHS Guidelines, July 2016.
Primary Care Meds Likely to Interact with HIV Meds

- Statins, other lipid lowering medications
- Select cardiovascular medications
- Inhaled corticosteroids
- Select psychotropics, narcotics, anti-gout meds
- BPH meds, ED medications
- Proton pump inhibitors and H2 blockers
- Rifampin/rifabutin
- Herbal Therapy
PRIMARY CARE DRUG INTERACTIONS WITH HIV MEDS
Case #1

- Patient stable on Kaletra+Raltegravir
- Started on Atorvastatin 80mg HS after vascular procedure, discharged to short term rehab facility
- Back in 2 weeks, acute renal failure, rhabdomyolysis
- What happened here?
Statins and Protease Inhibitors

- Simvastatin and lovastatin considered contraindicated with ALL protease inhibitors
- Safest statins are pravastatin, pitavastatin
  - Lowest pravastatin dose with darunavir/ritonavir
- Atorvastatin – Initiate at low doses, titrate, caution if >20mg
  - Do NOT co-administer with tipranavir/rtv
- Rosuvasstatin – Initiate at low doses, titrate
- All statins – monitor CPK, myalgias, LFTs
Statins and Protease Inhibitors

- Simvastatin and lovastatin considered contraindicated with ALL protease inhibitors
- Safest statins are pravastatin, pitavastatin
- Atorvastatin – Initiate at low doses, titrate, caution if >20mg
  - Do NOT co-administer with tipranavir/rtv
- Rosuvastatin – Initiate at low doses, titrate
- All statins – monitor CPK, myalgias, LFTs
Statins and Protease Inhibitors

- Pitavastatin
- 12 week randomized, blinded trial
- Pitavastatin 4 mg vs Pravastatin 40 mg
- LDL-C 130-220 mg/dL, TG ≤ 400 after 4 wk washout/dietary stabilization period
- N = 126/arm
- Baseline LDL-C 155, TC 238, TG 174, HDL 49
# Statins and Protease Inhibitors

<table>
<thead>
<tr>
<th>Metric</th>
<th>Pitavastatin</th>
<th>Pravastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C</td>
<td>-31.0%</td>
<td>-20.9% *</td>
</tr>
<tr>
<td>TG</td>
<td>-3.2%</td>
<td>-3.6%</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>-20.4%</td>
<td>-13.8% *</td>
</tr>
<tr>
<td>HDL-C</td>
<td>4.7%</td>
<td>5.7%</td>
</tr>
<tr>
<td>Non-HCL-C</td>
<td>-26.9%</td>
<td>-18.7%</td>
</tr>
</tbody>
</table>

* p < 0.001

- Similar adverse events
Case #2

- Patient admitted to outside hospital for Acute Coronary Syndrome,
- Long history of HIV, though controlled on Etravirine + Raltegravir + Tenofovir + Emtricitabine
- Undergoes PCI, has 3 stents placed
- Discharge meds include new Rxs for Prilosec and Plavix
- Any problems here?
<table>
<thead>
<tr>
<th>Drug</th>
<th>ASA</th>
<th>Clopidogrel (Plavix®)</th>
<th>Prasugrel (Effient®)</th>
<th>Ticagrelor (Brilinta®)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indications</strong></td>
<td>- 1° and 2° prevention of stroke and MI</td>
<td>- ASA intolerance or failure</td>
<td>- With ASA, for treatment of ACS in patients treated with PCI</td>
<td>- With ASA, for treatment of ACS See BCHA restrictions below¹</td>
</tr>
<tr>
<td></td>
<td>- ACS</td>
<td>- 1° and 2° prevention of stroke and MI (+/- ASA)</td>
<td>Contraindicated if: age &gt; 75 years; OR wt &lt; 60 kg; OR history of stroke</td>
<td>NON-FORMULARY</td>
</tr>
<tr>
<td></td>
<td>- PCI with stent</td>
<td>- ACS (+ ASA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- PVD</td>
<td>- PCI (+ ASA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- PVD</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dose and Duration</strong></td>
<td>Load: 160-325 mg Maintenance: 80 or 81 mg daily</td>
<td>Load: 300-600 mg Maintenance: 75 mg daily</td>
<td>Load: 60 mg Maintenance: 10 mg daily</td>
<td>Load: 180 mg Maintenance: 90 mg BID</td>
</tr>
<tr>
<td></td>
<td>Duration: Indefinite</td>
<td>Duration: ACS: up to 1 year</td>
<td>Duration: up to 1 year</td>
<td>Duration: up to 1 year</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BMS: minimum 30 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>DES: minimum 1 year</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Class</strong></td>
<td>Non-Steroidal Anti-Inflammatory Agent</td>
<td>Second generation thienopyridine (Prodrug)</td>
<td>Third-generation thienopyridine (Prodrug)</td>
<td>Cyto-pentyl-triazolo-pyrimidine</td>
</tr>
<tr>
<td><strong>Mechanism of Platelet Inhibition</strong></td>
<td>Irreversible inhibitor of COX-1 causing decrease in thromboxane A₂</td>
<td>Irreversible inhibitor of P2Y₁₂ component of ADP receptor (preventing ADP binding and activation of platelets)</td>
<td>Irreversible inhibitor of P2Y₁₂ component of ADP receptor (preventing ADP binding and activation of platelets)</td>
<td>Reversibly modifies P2Y₁₂ component of ADP receptor (preventing ADP binding and activation of platelets)</td>
</tr>
<tr>
<td><strong>Oral Bioavailability</strong></td>
<td>50-75%</td>
<td>&gt; 50% (active metabolite)</td>
<td>&gt; 78% (active metabolite)</td>
<td>30-42%</td>
</tr>
<tr>
<td><strong>Peak Effect</strong></td>
<td>1-3 hours</td>
<td>6 hours (after load)</td>
<td>4 hours (after load)</td>
<td>2 hours (after load)</td>
</tr>
<tr>
<td><strong>Half-life (active metabolite)</strong></td>
<td>3 hrs (salicylate)</td>
<td>0.5 hrs</td>
<td>7 hrs (range 2-15 hrs)</td>
<td>9 hrs (range 6.7-9.1 hrs)</td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
<td>Hydrolyzed by esterases; Hepatic conjugation</td>
<td>Esterases; Metabolism by CYP-450 enzymes</td>
<td>Esterases; Metabolism by CYP-450 enzymes</td>
<td>Metabolism by CYP-450 enzymes</td>
</tr>
<tr>
<td><strong>CYP Metabolism</strong></td>
<td>No</td>
<td>CYP2C19</td>
<td>CYP3A4, CYP2B6</td>
<td>CYP3A4/5</td>
</tr>
<tr>
<td><strong>When to Hold Dose Prior to Surgery</strong></td>
<td>7 days (optional)</td>
<td>5-7 days</td>
<td>7 days</td>
<td>5 days</td>
</tr>
</tbody>
</table>
Anti-platelet Meds

- Clopidogrel (Plavix) – used commonly post-stent after PCI
  - Requires activation to an active metabolite via CYP2C19
- Prasugrel (Effient) – used commonly post-stent after PCI
  - Also requires activation to an active metabolite, but via CYP3A4 and 2B6 primarily
- Etravirine is a mild inducer of CYP3A4, but also inhibits CYP2C19
  - By inhibiting the action of 2C19, likely to get less production of the active metabolite for Plavix
- Prasugrel may be a better choice in this situation, theoretically
- Similar issue with the PPI omeprazole (also metabolized via 2C19), no significant effect with dexlansoprazole, lansoprazole, or pantoprazole
- Safest NNRTI with this class is rilpivirine
Anti-platelet Meds

• Prasugrel (Effient)
  • Also requires activation to an active metabolite, but via CYP3A4 and 2B6 primarily
  • If on a PI, similar interaction with prasugrel expected, since less metabolite produced, though unclear significance, about 35% reduction in metabolite

• Ticagrelor (Brilinta), shortest activation time
  • Healthy volunteer data with ketoconazole > AUC of ticagrelor 632%
  • Strong CYP3A inhibitors contraindicated
Other Anticoagulants?

- Warfarin (Coumadin)
- Dabigatran (Pradaxa)
- Rivaroxaban (Xarelto)
- Apixaban (Eliquis)
- Enoxaban (Savaysa)
<table>
<thead>
<tr>
<th></th>
<th>Warfarin</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Dabigatran etexilate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>Vitamin K epoxide reductase (reducing the vitamin K dependent coagulation factors)</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
<td>Thrombin</td>
</tr>
<tr>
<td>T (max)</td>
<td>72-96 h</td>
<td>2.5-4 h</td>
<td>3 h</td>
<td>2 h</td>
</tr>
<tr>
<td>Half-life</td>
<td>40 h</td>
<td>5-9 h healthy, 9-13 h elderly</td>
<td>8-15 h</td>
<td>14-17 h</td>
</tr>
<tr>
<td>Monitoring</td>
<td>INR-adjusted</td>
<td>Not needed</td>
<td>Not needed</td>
<td>Not needed</td>
</tr>
<tr>
<td>Administration</td>
<td>Once daily</td>
<td>Once daily</td>
<td>Twice daily</td>
<td>Once or twice daily</td>
</tr>
<tr>
<td>Metabolism</td>
<td>CYP P450</td>
<td>66% fecal, 33% renal</td>
<td>75% fecal, 25% renal</td>
<td>80% renal, 20% fecal</td>
</tr>
<tr>
<td>Drug Interactions</td>
<td>CYP 2C9, 1A2, and 3A4 inhibitors</td>
<td>Potent CYP 3A4 inhibitors</td>
<td>Potent CYP 3A4 inhibitors decrease absorption</td>
<td>Proton pump inhibitors and P-gp inhibitor decrease absorption</td>
</tr>
</tbody>
</table>

Table is modified from Zikria and Ansell, 2009. T (max): peak plasma levels; h: hours; INR: international normalized ratio; PT: prothrombin time; CYP: Cytochrome P; P-gp transporters: P-glycoprotein transporters.
Dabigatran Drug Interactions

- P-glycoprotein inhibitors
  - E.g. Verapamil, amiodarone, quinidine, clarithromycin
  - No dose adjustments are necessary
    - Avoid if CrCl < 30 ml/min
  - Ketoconazole and dronadarone
    - CrCl 30 – 50 ml/min
    - Dabigatran 75mg PO twice a day
  - **What does that mean for ritonavir, other PIs, cobicistat?**

- P-glycoprotein inducers
  - E.g. Rifampin, carbamazepine
  - Inducers should be avoided
## Rivaroxaban – Drug Interactions

<table>
<thead>
<tr>
<th>P-glycoprotein/ Strong 3A4 inhibitors</th>
<th>Less potent P-glycoprotein/3A4 inhibitors</th>
<th>P-glycoprotein/ Strong 3A4 inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Agents:</strong></td>
<td><strong>Agents:</strong></td>
<td><strong>Agents:</strong></td>
</tr>
<tr>
<td>Conivaptan, itraconazole, ketoconazole, lopinavir/ritonavir, ritonavir</td>
<td>Azithromycin, clarithromycin, diltiazem, dronaderone, erythromycin, verapamil</td>
<td>Carbamazepine, phenytoin, rifampin, St. John’s Wort</td>
</tr>
<tr>
<td><strong>Management:</strong></td>
<td><strong>Management:</strong></td>
<td><strong>Management:</strong></td>
</tr>
<tr>
<td>- Avoid combination</td>
<td>- Do not use combination in mild renal impairment (CrCl 30 – 60ml/min)</td>
<td>- Avoid combination if possible</td>
</tr>
</tbody>
</table>

# Apixaban – Drug Interactions

<table>
<thead>
<tr>
<th>P-glycoprotein/Strong 3A4 inhibitors</th>
<th>P-glycoprotein/Strong 3A4 inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Agents:</strong></td>
<td><strong>Agents:</strong></td>
</tr>
<tr>
<td>Itraconazole, ketoconazole, ritonavir, clarithromycin</td>
<td>Carbamazepine, phenytoin, rifampin, St. John’s Wort</td>
</tr>
<tr>
<td><strong>Management:</strong></td>
<td><strong>Management:</strong></td>
</tr>
<tr>
<td>- Decrease dose to 2.5mg PO twice a day</td>
<td>- Avoid combination</td>
</tr>
<tr>
<td>- If patient is already on 2.5mg, avoid combination</td>
<td></td>
</tr>
</tbody>
</table>
## Cardiovascular Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>PK Interaction</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiarrhythmics</td>
<td>• Lack of PK data&lt;br&gt;• CYP-450 involvement&lt;br&gt;• Potential for ↑ exposure</td>
<td>• Potential toxicity of antiarrhythmics&lt;br&gt;• Use with caution&lt;br&gt;• Monitor for QT prolongation</td>
</tr>
<tr>
<td>Warfarin</td>
<td>• Lack of PK data&lt;br&gt;• CYP-450 involvement&lt;br&gt;• Potential for ↑ or ↓ exposure of warfarin</td>
<td>• Potential warfarin toxicity or reduced efficacy&lt;br&gt;• Monitor INR closely</td>
</tr>
<tr>
<td>CCBs</td>
<td>• ↑ exposure of diltiazem with ATV unboosted&lt;br&gt;• potential for ↑ exposure of CCBs with other PIs and cobicistat</td>
<td>• potential CCB-associated toxicity&lt;br&gt;• ↓ diltiazem dose by ½ with ATV&lt;br&gt;• monitor ECG and for CCB-associated toxicity with all PIs and cobicistat</td>
</tr>
</tbody>
</table>
## Cardiovascular Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>PK Interaction</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta blockers</td>
<td>• Potential for ↑ exposure of metoprolol and timolol with PIs (no PK data)</td>
<td>• potential for toxicity of beta-blockers which are metabolized by CYP-450</td>
</tr>
<tr>
<td></td>
<td>• negligible effect on atenolol when administered with ATV</td>
<td>• monitor for beta-blocker-associated toxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• may use atenolol safely with ATV (&amp; likely with other PIs, no data)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>• ↑ exposure of digoxin when administered with RTV, SQV/r, DRV/r</td>
<td>• potential for digoxin toxicity</td>
</tr>
<tr>
<td></td>
<td>• p-glycoprotein inhibition by RTV</td>
<td>• monitor digoxin concentrations closely</td>
</tr>
<tr>
<td></td>
<td>• Likely with other boosted PIs as well</td>
<td>• monitor for digoxin-associated toxicity</td>
</tr>
</tbody>
</table>

DHHS Guidelines, July 2016
<table>
<thead>
<tr>
<th>Drug</th>
<th>Alternate Name</th>
<th>Dose</th>
<th>Route</th>
<th>Freq</th>
<th>Chart Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLONAZEPAM</td>
<td>KLOPONIN</td>
<td>0.5 MG = 1 TAB</td>
<td>ORAL</td>
<td>Q8HR</td>
<td>ADMIN</td>
</tr>
<tr>
<td>SERTRALINE</td>
<td>ZOLOFT</td>
<td>50 MG = 1 TAB</td>
<td>ORAL</td>
<td>1XDAY</td>
<td>ADMIN</td>
</tr>
<tr>
<td>RALTEGRAVIR</td>
<td>ISENTRESS</td>
<td>400 MG = 1 TAB</td>
<td>ORAL</td>
<td>2XDAY</td>
<td>ADMIN</td>
</tr>
<tr>
<td>RITONAVIR</td>
<td>NORVIR</td>
<td>100 MG = 1 TAB</td>
<td>ORAL</td>
<td>1XDAY</td>
<td>ADMIN</td>
</tr>
<tr>
<td>EMTRICITAB-</td>
<td>TRUVADA 200-300MG</td>
<td>1 TAB = 1 TAB</td>
<td>ORAL</td>
<td>1XDAY</td>
<td>ADMIN</td>
</tr>
<tr>
<td>DARUNAVIR</td>
<td>PREZISTA</td>
<td>800 MG = 1 TAB</td>
<td>ORAL</td>
<td>1XDAY</td>
<td>ADMIN</td>
</tr>
<tr>
<td>ENOXAPARIN</td>
<td>LOVENOX</td>
<td>40 MG = 0.4 ML</td>
<td>SUBCUT</td>
<td>1XDAY 0800</td>
<td>ADMIN</td>
</tr>
<tr>
<td>LISINOPRIL</td>
<td>ZESTRIL</td>
<td>10 MG = 1 TAB</td>
<td>ORAL</td>
<td>1XDAY</td>
<td>ADMIN</td>
</tr>
<tr>
<td>ISOSORBIDE MONONITRATE</td>
<td>IMDUR</td>
<td>60 MG = 1 TAB</td>
<td>ORAL</td>
<td>1XDAY</td>
<td>NOTADMI</td>
</tr>
<tr>
<td>METOPROLOL TARTRATE</td>
<td>LOPRESSOR</td>
<td>25 MG = 1 TAB</td>
<td>ORAL</td>
<td>2XDAY</td>
<td>ADMIN</td>
</tr>
<tr>
<td>NICOTINE PATCH (MG/24H)</td>
<td>NICODERM CQ</td>
<td>21 MG = 1 PATCH</td>
<td>TRANSFER</td>
<td>1XDAY</td>
<td>ADMIN</td>
</tr>
<tr>
<td>GLYBURIDE/METFORMIN</td>
<td>GLYBURIDE/METFORM</td>
<td>5 MG/500MG</td>
<td>ORAL</td>
<td>2XDAY</td>
<td>NOTADMI</td>
</tr>
<tr>
<td>VITAMIN D2</td>
<td>ERGOCALCIFEROL</td>
<td>50000 UNITS = 1</td>
<td>ORAL</td>
<td>FRIDAY</td>
<td>ADMIN</td>
</tr>
<tr>
<td>GABAPENTIN</td>
<td>NEURONTIN</td>
<td>300 MG = 1 CAP</td>
<td>ORAL</td>
<td>3XDAY</td>
<td>ADMIN</td>
</tr>
<tr>
<td>FOLIC ACID</td>
<td>FOLIC ACID</td>
<td>1 MG = 1 TAB</td>
<td>ORAL</td>
<td>1XDAY</td>
<td>ADMIN</td>
</tr>
<tr>
<td>PANTOPRAZOLE</td>
<td>PROTONIX</td>
<td>40 MG = 1 TAB</td>
<td>ORAL</td>
<td>1XDAY 0600</td>
<td>ADMIN</td>
</tr>
<tr>
<td>BRIMONIDINE 0.2% OPTH</td>
<td>ALPHAGAN 0.2%</td>
<td>1 DROP = 1 DROP</td>
<td>BOTH</td>
<td>2XDAY</td>
<td>ADMIN</td>
</tr>
<tr>
<td>RANOLAZINE SR</td>
<td>RANEXA</td>
<td>500 MG = 1 TAB</td>
<td>ORAL</td>
<td>2XDAY</td>
<td>NOTADMI</td>
</tr>
<tr>
<td>ASPIRIN EC</td>
<td>ASPIRIN EC</td>
<td>325 MG = 1 TAB</td>
<td>ORAL</td>
<td>1XDAY</td>
<td>ADMIN</td>
</tr>
<tr>
<td>ROSUVASTATIN</td>
<td>CRESTOR</td>
<td>10 MG = 1 TAB</td>
<td>ORAL</td>
<td>BEDTIME</td>
<td>ADMIN</td>
</tr>
<tr>
<td>UMECLIDINUM INHALER</td>
<td>INCURSE ELLIPTA</td>
<td>62.5 MCG = 1 PUFF</td>
<td>INH</td>
<td>1XDAY</td>
<td>ADMIN</td>
</tr>
<tr>
<td>INSULIN ASPART PEN</td>
<td>NovoLOG Flexpen</td>
<td>SCALE</td>
<td>SUBCUT</td>
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<tr>
<td>LORAZEPAM</td>
<td>ATIVAN</td>
<td>1 MG = 0.5 ML</td>
<td>IV</td>
<td>Q6H PRN</td>
<td>NOTADMI</td>
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<tr>
<td>OXYCODONE - APAP 5-325</td>
<td>PERCOCET</td>
<td>2 TAB = 2 TAB</td>
<td>ORAL</td>
<td>Q4H PRN</td>
<td>ADMIN</td>
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<tr>
<td>ONDANSETRON</td>
<td>ZOFRAN</td>
<td>4 MG = 2 ML</td>
<td>IV</td>
<td>Q8H PRN</td>
<td>ADMIN</td>
</tr>
<tr>
<td>MORPHINE</td>
<td>MORPHINE</td>
<td>4 MG = 1 ML</td>
<td>IV</td>
<td>Q1H PRN</td>
<td>ADMIN</td>
</tr>
<tr>
<td>MORPHINE</td>
<td>MORPHINE</td>
<td>2 MG = 1 ML</td>
<td>IV</td>
<td>Q1H PRN</td>
<td>ADMIN</td>
</tr>
<tr>
<td>MORPHINE</td>
<td>MORPHINE</td>
<td>1 MG = 0.5 ML</td>
<td>IV</td>
<td>Q1H PRN</td>
<td>ADMIN</td>
</tr>
<tr>
<td>GI COCKTAIL FOR ER</td>
<td>ANTACID</td>
<td>40 ML = 40 ML</td>
<td>ORAL</td>
<td>ONE TIME</td>
<td>NOTADMI</td>
</tr>
<tr>
<td>LORAZEPAM</td>
<td>ATIVAN</td>
<td>0.5 MG = 0.25 ML</td>
<td>IV</td>
<td>ONE TIME</td>
<td>ADMIN</td>
</tr>
<tr>
<td>LORAZEPAM</td>
<td>ATIVAN</td>
<td>1 MG = 0.5 ML</td>
<td>IV</td>
<td>ADMIN</td>
<td>ADMIN</td>
</tr>
<tr>
<td>MORPHINE</td>
<td>MORPHINE</td>
<td>4 MG = 1 ML</td>
<td>IV</td>
<td>ADMIN</td>
<td>ADMIN</td>
</tr>
</tbody>
</table>
Inhaled Steroids and Protease Inhibitors

- Which steroids can we use with PIs?
- Ritonavir inhibits the metabolism of fluticasone
- Cushing’s syndrome reported with ritonavir-containing PI regimens and inhaled fluticasone:
  - Mean duration of fluticasone use was 75.5 weeks (range 20 days – 18 months)
- Case reports with oral and inhaled budesonide
- Recent reports with OCULAR dexamethasone
- Now cases reported with injectable steroids for joint inflammation – usually triamcinolone

Inhaled Steroids and Protease Inhibitors, Cobicistat

Nasal fluticasone
  - Switch to beclomethasone, possibly mometasone
Inhaled fluticasone or budesonide
  - Switch to beclomethasone
Salmeterol, contained in Advair®
  - Concurrent use of salmeterol and ritonavir to be avoided due to CV risk – tachycardia, QT prolongation, palpitations
  - Not clear if same risk exists for formoterol?
  - Consider safer steroid listed above alone, plus montelukast, plus rescue albuterol as needed
Combinations Dulera and Symbicort an issue as well

DHHS Guidelines, July 2016
Beclomethasone and DRV/rtv

- Beclomethasone inhaled alone, with RTV 100mg BID, and with DRV/RTV 600/100 mg twice daily
- Cosyntropin stim test at baseline and prior to adding regimens
- Baseline adrenal function (day 1) was compared to adrenal function during BDP treatment in the presence and absence of RTV or DRV/r
- No reductions in basal or peak cortisol levels at day 14, 28 or 42 in any group and no significant differences between groups at any time-point ($p >0.05$).
- Combined use of BDP and RTV or DRV/r for 28 days does not cause significant adrenal suppression in healthy volunteers.
- Inhaled BDP is preferable to inhaled fluticasone for treatment of HIV$^+$ patients receiving PI.

Proton Pump Inhibitors

- Proton pump inhibitors such as omeprazole, lansoprazole, esomperazole, etc.
- Atazanavir
  - Do not use if atazanavir unboosted
  - If ARV experienced, proton pump inhibitors not recommended
  - If ARV naïve and using atazanavir with ritonavir, can use up to the equivalent of omeprazole 20mg daily
- Rilpivirine, nelfinavir, delavirdine
  - Proton pump inhibitors not recommended at all
  - Contraindicated with rilpivirine, also Complera®, Odefsey®
H2 Blockers

- **Boosted Atazanavir**
  - H2 blockers simultaneously with and/or 10 hours after the H2 receptor antagonist (H2RA)
  - Maximum H2RA dose equivalent to famotidine 20mg BID for treatment-experienced, and 40mg BID for naives
- **Unboosted atazanavir**
  - Atazanavir given at least 2 hours before and at least 10 hours after the H2RA
  - Maximum H2RA dose equivalent to famotidine 20mg BID
  - Only acceptable in treatment naïve patients
- **Fosamprenavir**
  - Fosamprenavir given at least 2 hours before H2RA
Antidepressants

- **CONTRAINDICATED**
  - Fluvoxamine (Luvox®)
  - Nefazodone (Serzone®)

- Selective Serotonin Reuptake Inhibitors
  - Fluoxetine (Prozac®) & paroxetine (Paxil®, Pexeva®):
    - Interactions not clinically significant
    - Paroxetine (Paxil®) levels decreased by darunavir/rtv and fosamprenavir/rtv (about 50%)
  - Citalopram (Celexa®), escitalopram (Lexapro®), & sertraline (Zoloft®) have fewest interactions
    - Sertraline levels decreased by efavirenz and darunavir/ritonavir (about 50%)

- Tricyclic antidepressants
  - All boosted PIs and cobicistat expected to increase levels of TCAs
Antidepressants

- Dual-action agents:
  - Venlafaxine (Effexor®) & duloxetine (Cymbalta®)
  - Well tolerated without adjusting dose
  - Vilazodone (Viibryd®) likely to be increased by PIs
- Bupropion (Wellbutrin®, Zyban®)
  - AUC decreased 57% with lopinavir/rtv
  - AUC decreased 46% with tipranavir/rtv
- Mirtazapine (Remeron®)
  - Well tolerated, although some 3A4 metabolism
- Trazodone (Deseryl®)
  - With ritonavir-boosted PIs and cobicistat, start low, titrate
Benzodiazepines

- **CONTRAINDICATED with COBI and RTV**
  - Triazolam (Halcion®) and oral midazolam with PIs or cobicistat
  - Midazolam (Versed®) – Single dose for sedation acceptable if in a controlled environment

- Safest to use glucuronidated benzodiazepines (LOT)
  - Lorazepam (Ativan®)
  - Oxazepam (Serax®)
  - Temazepam (Restoril®)

- Use at lower doses & titrate
  - Alprazolam, clonazepam, diazepam

DHHS Guidelines, February 2016
Antipsychotics

- **CONTRAINDICATED**
  - Pimozide (Orap®)
  - Avoid chlorpromazine (Thorazine®), thioridazine (Mellaril®)
  - When used with ritonavir, start with lowest dose
    - Haloperidol (Haldol®) – risk of EPS & TD
    - Olanzapine (Zyprexa®), clozapine (Clozaril®), risperidone (Risperdal®)
- Metabolized by CYP3A4
  - Aripiprazole (Abilify®), ziprasidone (Geodon®), clozapine (Clozaril®) iloperidone, lurasidone
  - Quetiapine (Seroquel®), 6 fold elevation with LPV/r
  - Likely to be increased by protease inhibitors
Narcotics

• Fentanyl – HIGH dose ritonavir increased fentanyl
  – Low dose patches to start, titrate slow, monitor closely
  – Caution regarding recreational use and buccal absorption

• Hydrocodone, tramadol – Potential to be increased with ritonavir via CYP2D6 inhibition

• Oxycodone and LPV/r 400/100 twice daily
  – 2.6 fold increase in oxycodone levels (range 1.9-3.3 fold)
  – Likely similar with other PIs
  – Cobicistat? Mild CYP2D6 inhibitor
# Methadone and HIV Medications

<table>
<thead>
<tr>
<th>HIV Medication</th>
<th>Pharmacokinetic Information and Clinical Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir</td>
<td>Methadone clearance increased 22%; no change recommended</td>
</tr>
<tr>
<td>Stavudine</td>
<td>Stavudine AUC decreased 23%, Cmax decreased 44%; no change recommended</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>Zidovudine AUC increased 29% to 43%; monitor for zidovudine related adverse effects</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Methadone AUC decreased 52%; methadone withdrawal common; increased methadone dose likely required</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>Methadone AUC decreased 41%; methadone withdrawal common; increased methadone dose likely required</td>
</tr>
<tr>
<td>Fosamprenavir (unboosted)</td>
<td>No data; with amprenavir, R-methadone Cmin decreased 21%; Monitor and increase methadone as needed</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>Methadone AUC decreased 40%; methadone withdrawal rare; monitor and increased methadone as needed</td>
</tr>
</tbody>
</table>
# Methadone and HIV Medications

<table>
<thead>
<tr>
<th>HIV Medication</th>
<th>Pharmacokinetic Information and Clinical Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atazanavir/ritonavir</td>
<td>R methadone AUC decreased 16% to 18%; methadone withdrawal unlikely but possible; increase methadone dose as clinically indicated</td>
</tr>
<tr>
<td>Darunavir/ritonavir</td>
<td></td>
</tr>
<tr>
<td>Fosamprenavir/ritonavir</td>
<td></td>
</tr>
<tr>
<td>Lopinavir/ritonavir</td>
<td>Methadone AUC decreased 25% to 53%; methadone withdrawal unlikely but possible; increase methadone dose as clinically indicated</td>
</tr>
<tr>
<td>Saquinavir/ritonavir</td>
<td>R methadone AUC decreased 19%; methadone withdrawal unlikely but possible; increase methadone dose as clinically indicated</td>
</tr>
<tr>
<td>Tipranavir/ritonavir</td>
<td>R methadone AUC decreased 48%; methadone withdrawal unlikely but possible; increase methadone dose as clinically indicated</td>
</tr>
</tbody>
</table>
# Buprenorphine and HIV Medications

<table>
<thead>
<tr>
<th>HIV Medication</th>
<th>Pharmacokinetic Information and Clinical Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz</td>
<td>Buprenorphine AUC decreased 50%; norbuprenorphine AUC decreased 71%; no change recommended</td>
</tr>
<tr>
<td>Etravirine</td>
<td>Buprenorphine AUC decreased 25%, no change recommended</td>
</tr>
<tr>
<td>Atazanavir (unboosted)</td>
<td>Buprenorphine AUC increased 93%; norbuprenorphine AUC increased 76%; decreased atazanavir possible; do not co-administer</td>
</tr>
<tr>
<td>Atazanavir/rtv</td>
<td>Buprenorphine AUC increased 66%; norbuprenorphine AUC increased 105%; monitor for sedation, buprenorphine dosage reduction may need</td>
</tr>
<tr>
<td>Darunavir/rtv</td>
<td>Buprenorphine, no change; norbuprenorphine AUC increased 46%, Cmin increased 71%; no change recommended</td>
</tr>
<tr>
<td>Fosamprenavir/rtv</td>
<td>Buprenorphine, no change; norbuprenorphine AUC decreased 15%; no change recommended</td>
</tr>
<tr>
<td>Tipranavir/rtv</td>
<td>Buprenorphine, no change; norbuprenorphine decreased 80%; Tipranavir Cmin reduced 19% to 40%. Consider TPV TDM</td>
</tr>
</tbody>
</table>

www.nynjaetc.org
Colchicine (Colcrys®)

• Fatalities reported with concurrent use of colchicine and clarithromycin, a strong CYP3A4 inhibitor
• Increases in colchicine also expected with ritonavir-boosted protease inhibitors, ketoconazole, itraconazole
• Dosing if on a protease inhibitor + ritonavir
  – Acute attack – Max of 0.6mg, followed by 0.3mg (1/2 tab) one hour later. Do not repeat for 3 DAYS!
  – Prevention – cut dose in half – IE: if on 0.6mg daily, max per day is 0.3mg
• See insert for additional info – chart available in label, and in DHHS Drug Interaction Tables
BPH & HIV Meds

- Avodart (dutasteride)
  - Metabolized by CYP3A4, CONTRAINDIcATED in Norvir Label

- Uroxatral (alfuzosin)
  - Metabolized by CYP3A4, CONTRAINDIcATED with potent CYP3A4 inhibitors

- Cardura (doxazosin)
  - Metabolized by 3A4, drug levels can be increased PIs (esp. ritonavir)

- Flomax (tamsulosin)
  - Metabolized by CYP3A4 and CYP2D6, drug levels can be increased by PIs (esp ritonavir and in poor metabolizers)

- Detrol LA (tolteridine)
  - Not metabolized by 3A4
What’s UP? ED Meds

- All are CYP3A4 substrates
- Potential for hypotension, cardiac complications and abnormal vision if protease inhibitors used concomitantly
- Start with lowest possible doses with PIs, COBI
  - Viagra® (sildenafil): 25 mg q 48 hours
    - AUC ↑ 11-fold by ritonavir
  - Cialis® (tadalafil): 10 mg q 72 hours
    - AUC ↑ 125% by ritonavir
  - Levitra® (vardenafil): 2.5 mg q 72 hours
    - AUC ↑ 49-fold & 16-fold by Indinavir/rtv
- Avanafil – 13 fold increase with RTV 600mg BID not recommended with any boosted PI
- See DHHS Guidelines for PAH dosing
Rifampin and Rifabutin

- **Rifampin** – potent CYP450 inducer, contraindicated with PIs
  - Efavirenz – can use together, consider 800mg EFV (>60kg)
  - Raltegravir – increase RAL to 800mg BID
  - Etravirine, rilpivirine – not recommended
- **Rifabutin** – less potent inducer, but still problematic
  - All boosted PIs – 150mg **every day** or TIW
    - Most studies in healthy volunteers, consider
  - Efavirenz – Rifabutin 450-600mg daily or 600mg three times weekly if NOT on a boosted PI
  - Etravirine – if with a boosted PI, not recommended, otherwise, rifabutin 300mg once daily
  - Rilpivirine – not recommended

DHHS Guidelines, July 2016
Herbal Therapy

- St Johns Wort – contraindicated with all PIs
- Garlic – data with saquinavir showing a reduction in ARV levels, even after stopping
- Milk Thistle – interaction data with Darunavir/r showed no change needed
- Echinacea – data with etravirine – no interaction
- Ginseng – recent report of hepatotoxicity in a patient on Isentress, Kaletra

General statements
- Often no data with HIV meds
- Often capsules or tabs contain an herbal “mix”
- If patients insist on using an herbal with no data, simply separating from ARVs is important – may minimize the interaction

DHHS Guidelines, July 2016
Approach to Drug Interactions

- General Principles
  - Pick the path of least resistance
  - Be wary of new meds, read the Product Information
  - Be wary of consults writing for new meds
  - Be careful in hospital, ie hospitalist service not consulting HIV
- Most interactions have a clear answer, cut and dry PK data
- Some interaction has an answer for similar drugs with similar properties where we can at least make comparisons
- Some interaction has no answer, completely based upon clinical practice
- Use Resources
HELPFUL RESOURCES
Web Resources of Interest

- DHHS Guideline Tables
  - http://www.aidsinfo.nih.gov/guidelines/
- NY/NJ AIDS Education and Training Center
  - http://www.nynjaetc.org/
- University of Liverpool
  - www.hiv-druginteractions.org
- Toronto HIV Clinic
  - http://www.hivclinic.ca/main/home
www.hiv-druginteractions.org

LATEST ARTICLES
- Pharmacology of integrase inhibitors
- Lopinavir and eltrombopag
- 14th Workshop on HIV Comorbidities and ADRs, Washington
- Lopinavir/r and Pitavastatin
- Fluticasone, fluconazole and ritonavir interactions.

Click here for previous news items

SITE UPDATES
- ARVs for patients with swallowing difficulties.
- Expanded General Anaesthetics

SECTION The General Anaesthetics section has been expanded to include muscle relaxants and additional genera...

FOLLOW US ON TWITTER
For the latest additions and updates to the site, click the button to follow hivinteractions on Twitter.
www.hiv-druginteractions.org

Latest articles:

- Review - Pharmacology of integrase inhibitors
- Drug Interactions - Lopinavir and eltrombopag
- Meeting Report - 14th Workshop on HIV Comorbidities and ADRs, Washington
- Drug Interactions - Lopinavir/ and Pitavastatin
- Case Report - Fluticasone, fluconazole and ritonavir interactions.

Click here for previous news items

Site updates:

- ARVs for patients with swallowing difficulties.
As part of a national network of 11 regional and 3 national centers (and more than 100 associated sites) the NY/NJ AETC conducts targeted, multi-disciplinary education and training programs for healthcare providers treating people living with HIV/AIDS.

The NY/NJ AETC's mission is to assist health care professionals, through education and training, to provide optimum quality services and sensitive care to HIV positive persons, and to provide access to current research and treatment of HIV/AIDS. We serve the New York and New Jersey healthcare community by providing AIDS and HIV education and training to treat, manage, diagnose, or counsel individuals with HIV infection, or to help prevent high-risk behaviors that lead to HIV transmission.
As part of a national network of 11 regional and 3 national centers (and more than 100 associated sites) the NY/NJ AETC conducts targeted, multi-disciplinary education and training programs for healthcare providers treating persons living with HIV/AIDS.

The NY/NJ AETC's mission is to assist health care professionals, through education and training, to provide effective care for persons living with HIV/AIDS.
The NY/NJ AETC in collaboration with medical professionals periodically prepares, develops and disseminates clinical support tools. These products are designed as guides and are intended to provide quick and easy reference.

### Antiretroviral Guides

<table>
<thead>
<tr>
<th>CLINICAL SUPPORT TOOL</th>
<th>DESCRIPTION</th>
<th>HOW TO ORDER</th>
<th>LAST UPDATED</th>
<th>FORMAT AND SIZE</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV and HCV Drug Interactions: A Quick Guide for Providers</td>
<td>HCV guidelines</td>
<td>Available</td>
<td>February</td>
<td>PDF</td>
</tr>
<tr>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
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</tbody>
</table>
Helpful HIV Medication Tables for Pharmacists

Winter 2014
# Ledipasvir/Sofosbuvir (Harvoni®) Drug Interactions

## A Quick Guide for Clinicians – March 2016

John J Faragon, PharmD, BCPS, AAHIVP, Kristen Marks, MD, Marshall Glesby, MD, PhD, Douglas Fish, MD

### Mechanism of Action and Route of Metabolism for Ledipasvir/Sofosbuvir (Harvoni®)

<table>
<thead>
<tr>
<th>Medication</th>
<th>HCV Mechanism of Action</th>
<th>Route of Metabolism and Drug Interaction Potential</th>
</tr>
</thead>
</table>
| Ledipasvir/Sofosbuvir (Harvoni®)  | NS5a inhibitor and NS5b polymerase inhibitor | • Ledipasvir is an inhibitor of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Unknown metabolism via slow oxidative metabolism has been observed.  
• Sofosbuvir is a substrate for P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). The intracellular metabolism of sofosbuvir is enhanced by inhibition of CYP3A. |

### Ledipasvir/Sofosbuvir (Harvoni®) Drug Interactions with HIV Medications

<table>
<thead>
<tr>
<th>Concurrent Medication</th>
<th>Recommendation and Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HIV Protease Inhibitors</strong></td>
<td></td>
</tr>
<tr>
<td>Atazanavir (Reyataz®) + ritonavir (Norvir®)</td>
<td>• HIV/HCV co-infection studies to date have not included patients receiving boosted HIV PIs</td>
</tr>
</tbody>
</table>
| Darunavir (Prezista®) + ritonavir (Norvir®)  | • Increase in tenofovir levels when used with ledipasvir. Ritonavir boosted protease inhibitors used for HIV have also been shown to increase tenofovir levels.  
  • A ritonavir boosted HIV protease inhibitor with tenofovir and ledipasvir may increase risk of tenofovir induced renal toxicity.  
  • Use alternative HCV therapy or change HIV antiretroviral therapy that does not include tenofovir  
  • If unable to change therapy and co-administration required, monitor for tenofovir-associated renal adverse events. |
| Lopinavir/ritonavir (Kaletra®)               |                                                                                                        |
| Fosamprenavir (Lexiva®) + ritonavir (Norvir®)|                                                                                                       |
| Saquinavir (Invirase®) + ritonavir (Norvir®) |                                                                                                        |
| Tipranavir (Aptivus®) + ritonavir (Norvir®)  | • Co-administration of ledipasvir/sofosbuvir with tipranavir + ritonavir may decrease the concentration of ledipasvir and sofosbuvir, leading to reduced effectiveness.  
  • Co-administration not recommended. |
### Drug Interactions with Oral Contraceptives and HIV Medications 2015

**John J Faragon, PharmD, BCPS, AAHIVP**

<table>
<thead>
<tr>
<th>ARV</th>
<th>Effect on Contraceptive</th>
<th>Recommendation with Oral Contraceptive</th>
<th>Recommendation with DMPA</th>
<th>Recommendation with Etonogestrel Implant</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NNRTIs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Efavirenz      | Ethinyl Estradiol/ Norgestimate:  
- No change in ethinyl estradiol  
- ↓ active metabolites of norgestimate  
- levonorgestrel AUC ↓ 83%;  
- norelgestromin AUC ↓ 64%  
Implant:  
- ↓ etonogestrel  
Emergency Contraception:  
- Levonorgestrel AUC ↓ 58% | Use alternative contraceptive method.                                                   | No additional contraceptive needed.    | Use alternative or additional contraceptive method. |
| Etravirine     | Ethinyl estradiol:  
- AUC ↑ 22%  
Norethindrone  
- No significant change | No additional contraceptive needed.                                                   | No additional contraceptive needed.    | No additional contraceptive needed.     |
| Nevirapine     | Ethinyl estradiol:  
- AUC ↓ 20%  
Norethindrone:  
- AUC ↓ 19%  
DMPA:  
- No significant change | Consider alternative method or reliable barrier contraception in addition.              | No additional contraceptive needed.    | Consider alternative method or reliable barrier contraception in addition. |
| Rilpivirine    | Ethinyl estradiol:  
- AUC ↑ 14%  
Norethindrone:  
- No significant change | No additional contraceptive needed.                                                   | No additional contraceptive needed.    | No additional contraceptive needed.     |
The AIDS Education and Training Center (AETC) Program supports the National HIV/AIDS Strategy by building clinician capacity and expertise along the HIV care continuum.
Drug Interaction Charts

<table>
<thead>
<tr>
<th>Step</th>
<th>Instructions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Choose one or more HEP drugs</td>
</tr>
<tr>
<td>2</td>
<td>Choose one or more combination classes</td>
</tr>
<tr>
<td>3</td>
<td>Choose one or more combination drugs</td>
</tr>
<tr>
<td>4</td>
<td>View results</td>
</tr>
</tbody>
</table>

**HCV Protease Inhibitors**
- ✅ Telaprevir
- Boceprevir

**Interferons**
- ✅ Peg-IFN alfa

**Nucleoside/tide Analogues**
- ✅ Ribavirin
- Entecavir
- Adefovir
- Lamivudine
DHHS Guidelines, 2016

<table>
<thead>
<tr>
<th>HCV Direct-Acting Antiviral Agents</th>
<th>HCV Non-Direct-Acting Antiviral Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NS5B Inhibitor</strong></td>
<td><strong>HCV Protease Inhibitors</strong></td>
</tr>
<tr>
<td>Sofosbuvir</td>
<td>Ledipasvir/Sofosbuvir</td>
</tr>
<tr>
<td></td>
<td>Simeprevir</td>
</tr>
<tr>
<td>No Longer Recommended by HCV Guidelines</td>
<td>Boceprevir</td>
</tr>
</tbody>
</table>
|                                  | Telaprevir (Discontinued from U.S. market in October 2014) | Ribavirin
|                                  |                                        | Pegylated interferon alpha |

**Integrate Strand Transfer Inhibitors**

<table>
<thead>
<tr>
<th>ETR</th>
<th>DTG</th>
<th>EVG/coh/ TDF/FTC</th>
<th>EVG + (P/r without cobi)</th>
<th>Refer to recommendations for specific ritonavir-boosted PI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>✓</td>
<td>✗</td>
<td>✓</td>
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</tr>
<tr>
<td>NVP</td>
<td>✓</td>
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<td>✓</td>
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<tr>
<td>RAL</td>
<td>✓</td>
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</tr>
<tr>
<td>RPV</td>
<td>✓</td>
<td>✓</td>
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</table>
Questions/Contact

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Please contact me with questions