Update on HIV: A Pharmacist’s Perspective

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Learning Objectives

- To review:
  - general principles of HIV/AIDS and HIV drug therapy
  - pertinent HIV drug therapy counseling points
  - common drug-drug interactions involving HIV meds
  - useful HIV drug therapy resources
HIV Drug Therapy Overview
What is HIV/AIDS?

- HIV: Human Immunodeficiency Virus
  - Single-stranded RNA retrovirus
  - Attacks the immune system and destroys T-cell lymphocytes or CD4 cells
  - CD4 cells regulate cell-mediated immunity and a decline will weaken immune system and make the body vulnerable to infections and cancers

- AIDS: Acquired Immune Deficiency Syndrome
  - CD4 < 200 cells/uL (or CD4% < 14%) OR presence of one or more AIDS-defining illness (eg. PCP, esophageal candidiasis, TB, CMV, etc)
HIV Transmission

- Body fluids:
  - blood
  - semen
  - vaginal fluids
  - breast milk

- Unprotected sex (anal, vaginal), Injection drug use, Mother-to-child transmission (pregnancy, breastfeeding), blood transfusions (hemophilia)
Typical Course of HIV Infection

CD4+ T Lymphocyte Count (cells/mm³)

- Primary infection
- Clinical Latency
- Opportunistic diseases
- Constitutional symptoms
- Death

HIV RNA Copies per ml Plasma

Classes of Antiretrovirals (ARVs):

- Entry Inhibitors
- Fusion Inhibitors
- Nucleoside Reverse Transcriptase Inhibitors (NRTIs)
- Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)
- Integrase Inhibitors (IIs)
- Protease Inhibitors (PIs)
What is HAART?

- **HAART**: Highly Active Antiretroviral Therapy
  - ARVs used in combination to maximize efficacy
    - Usually 3 different ARVs from 2 different classes
      - Ie. 2 NRTIs + PI or NNRTI or II
  - Suppress HIV-RNA viral load (prevents HIV multiplication) and allows for reconstitution of immune system (CD4 cells)
    - Goals on tx = “undetectable” or <40 copies/mL

- Must be taken all together (all or none)
- Must be taken every day (>95% adherence required for maximal suppression)
Trends in Annual Age-Adjusted* Rate of Death due to HIV Disease, United States, 1987–2006
Figure 1. Antiretroviral adherence and virologic suppression. Adapted from Paterson et al. Ann Intern Med. 2000;133:21-30.[6]
## Common Adherence Issues

<table>
<thead>
<tr>
<th>Issue</th>
<th>Potential Solution</th>
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</thead>
<tbody>
<tr>
<td>Adverse Effects</td>
<td>Tx symptoms, switch regimen</td>
</tr>
<tr>
<td>Difficulty swallowing large pills</td>
<td>RTV tablet now available Change regimen, liquid formulations, split/crush pills</td>
</tr>
<tr>
<td>Forgetfulness</td>
<td>Adherence tools (ie. blister pack, dosett, alarms, cell phones)</td>
</tr>
<tr>
<td>Not filling prescriptions properly</td>
<td>Understand problem – drug coverage, refills</td>
</tr>
<tr>
<td>Inadequate understanding of drug resistance/adherence</td>
<td>Educate, use resources including graphs/pictures for reading level and/or language</td>
</tr>
<tr>
<td>Nonadherence to food requirements</td>
<td>Access to food, timing of medications Switch regimen</td>
</tr>
<tr>
<td>Too many missed doses/incorrect timing</td>
<td>Adherence tools to help with same time of day administration, simplify regimen</td>
</tr>
</tbody>
</table>
Drug Resistance

- Suboptimal drug levels
  - Adherence
  - Malabsorption
  - Drug interactions
  - Not taking all drugs together

- Baseline resistance/transmitted resistance (~10%)

- Resistance testing (genotyping)
  - Completed at baseline and viral breakthrough
Goals of Antiretroviral Therapy

- Reduce HIV-associated morbidity and prolong duration and quality of survival
- Restore and preserve immunologic function
- Maximally and durably suppress HIV-1 RNA
  - Persistently below level of detection (< 20-75 copies/mL, depending on the assay used)
  - Isolated “blips” not uncommon in successfully treated patients and not thought to predict virologic failure
- Prevent HIV transmission

DHHS Guidelines for Antiretroviral Therapy in Adults and Adolescents. March 2012.
ART for HIV Prevention: The Hypothesis

- The quantity of HIV in plasma (and genital secretions) is the prime determinant of whether someone with HIV will transmit the virus to a sexual partner[1]
- Initiation of ART results in early and sustained reductions in plasma and genital HIV levels
- Led to the hypothesis that ART use would result in decreased infectiousness

HPTN 052: Immediate vs Delayed ART for HIV Prevention in Serodiscordant Couples

HIV-infected, sexually active serodiscordant couples; CD4+ cell count of the infected partner: 350-550 cells/mm³ (N = 1763 couples)

**Immediate ART**
Initiate ART at CD4+ cell count 350-550 cells/mm³ (n = 886 couples)

**Delayed ART**
Initiate ART at CD4+ cell count ≤ 250 cells/mm³* (n = 877 couples)

*Based on 2 consecutive values ≤ 250 cells/mm³.

- Primary efficacy endpoint: virologically linked HIV transmission
- Primary clinical endpoints: WHO stage IV events, pulmonary TB, severe bacterial infection and/or death
- Couples received intensive counseling on risk reduction and use of condoms

HPTN 052: HIV Transmission Reduced by 96% in Serodiscordant Couples

Total HIV-1 Transmission Events: 39
(4 in immediate arm and 35 in delayed arm; \( P < .0001 \))

Linked Transmissions: 28
- Delayed Arm: 27
- Immediate Arm: 1
  \( P < .001 \)

Unlinked or TBD Transmissions: 11

96% reduction in risk of HIV transmission within the partnership (95% CI: 73% to 99%)

HIV, ARVs, and Life Expectancy

- Life expectancy of 20-yr old HIV+ve on ART in US or Canada approaching that of general population
  - North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD)
  - 22,937 participants
  - > 20 yrs of age
  - initiating ART
  - January 1, 2000 – December 31, 2007

Samji et al. PLOS ONE 8(12):e81355 2014
### CD4 cell count at start of ART (cells/mm³):
- < 350 = 16,615
- ≥350 = 6,322 (28%)
Changing Criteria for Antiretroviral Therapy Initiation in DHHS Guidelines

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<tbody>
<tr>
<td>&gt; 500</td>
<td>Offer if VL &gt; 20K</td>
<td>Offer if VL &gt; 55K</td>
<td>Consider if VL ≥ 100K</td>
<td>Consider in certain groups*</td>
<td>Consider†</td>
<td>Treat</td>
</tr>
<tr>
<td>350-500</td>
<td>Offer if VL &gt; 20K</td>
<td>Consider if VL &gt; 55K</td>
<td>Consider if VL ≥ 100K</td>
<td>Consider in certain groups*</td>
<td>Treat</td>
<td>Treat</td>
</tr>
<tr>
<td>200-350</td>
<td>Offer if VL &gt; 20K</td>
<td>Offer, but controversy exists</td>
<td>Offer after discussion with patient</td>
<td>Treat</td>
<td>Treat</td>
<td>Treat</td>
</tr>
<tr>
<td>&lt; 200 or symptomatic</td>
<td>Treat</td>
<td>Treat</td>
<td>Treat</td>
<td>Treat</td>
<td>Treat</td>
<td>Treat</td>
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</table>

*Pregnant women, patients with HIV-associated nephropathy, and patients with HBV that requires treatment.
†50% of panel members recommended starting antiretroviral therapy; 50% of members viewed treatment as optional.

Considerations When Selecting First-line Antiretroviral Therapy

Patient/Viral Factors
- Baseline CD4+ cell count/HIV-1 RNA level
- Age
- Sex
- Occupation (e.g., work schedule)
- Comorbid conditions (e.g., CV risk)
- Plans for pregnancy
- Access to care
- Concurrent medications
- Adherence to other medications
- Genetics (e.g., HLA-B*5701)
- Viral tropism

Antiretroviral Drug Factors
- Efficacy
- Baseline drug susceptibility/resistance
- Tolerability
- Long-term toxicity, metabolic effects
- Drug interactions
- Dosing frequency
- Pill burden
- Pharmacokinetics
- Cost
# DHHS May 2014: What to Start

<table>
<thead>
<tr>
<th>For All Pts, Regardless of BL VL or CD4+ Count</th>
<th>Only for Pts With Pre-ART VL &lt; 100,000 c/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NNRTI</strong></td>
<td><strong>EFV + ABC/3TC</strong>*</td>
</tr>
<tr>
<td>▪ EFV/TDF/FTC</td>
<td>▪ RPV/TDF/FTC†</td>
</tr>
<tr>
<td><strong>Boostered PI</strong></td>
<td><strong>ATV/RTV + ABC/3TC</strong>*</td>
</tr>
<tr>
<td>▪ ATV/RTV + TDF/FTC</td>
<td>▪ DRV/RTV + TDF/FTC</td>
</tr>
<tr>
<td><strong>INSTI</strong></td>
<td></td>
</tr>
<tr>
<td>▪ RAL + TDF/FTC</td>
<td></td>
</tr>
<tr>
<td>▪ EVG/CQBI/TDF/FTC</td>
<td></td>
</tr>
<tr>
<td>▪ DTG + ABC/3TC*</td>
<td></td>
</tr>
<tr>
<td>▪ DTG + TDF/FTC</td>
<td></td>
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</tbody>
</table>

*Only for pts who are HLA-B*5701 negative. †Only for those with CD4+ cell counts > 200 cells/mm³.

DHHS guidelines. May 2014.
Concept Review: ARV Pharmacokinetic Enhancers
# Ritonavir vs. Cobicistat

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cobicistat</th>
<th>Ritonavir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enzyme inhibition effects</td>
<td>CYP 3A4, CYP 2D6 (weak)</td>
<td>CYP 3A4, CYP 2C8, CYP 2C9, CYP 2D6, P-gp</td>
</tr>
<tr>
<td>Enzyme induction</td>
<td>--</td>
<td>CYP 2B6, CYP 2C9, CYP 2C19, UGT 1A4, P-gp</td>
</tr>
<tr>
<td>Intrinsic anti-HIV activity</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Ability to co-formulate with other ARVs</td>
<td>Yes b/c COBI is highly soluble which facilitates co-formulation</td>
<td>Limited (only RTV-boosted lopinavir is available d/t stability &amp; compatibility issues)</td>
</tr>
</tbody>
</table>
Ritonavir (RTV)

- RTV = protease inhibitor originally dosed at 1200 mg/day to treat HIV
- Nowadays, administered at low doses (ie. 100-200mg/day) to boost the systemic concentrations of other HIV protease inhibitors
- Major limitations of RTV:
  - GI disturbances (diarrhea) and increased lipids
  - Inability to co-formulate means increased pill burden
Cobicistat (COBI)

- Novel pharmacokinetic booster agent
- COBI impacts the normal function of adipocytes less than RTV, thereby limiting lipid level elevations and insulin resistance
- COBI causes ↑ SCr via inhibition of renal tubular creatinine secretion but no actual ↓ in renal function
  - Similar to the false ↑ in SCr caused by trimethoprim
- Currently COBI is NOT available commercially in Canada as a single entity product
  - COBI 150mg is part of Stribild, to boost elvitegravir concentrations
  - COBI studied as a booster for darunavir and atazanavir

Pharmacotherapy 2013;33(10):1107-1116
Counseling Points for Common ARVs
**Tenofovir**

- Standard dose = 300mg once daily
  - CrCl less than 50mL/min ➔ less frequent dosing intervals

- Available as:
  - Tenofovir disoproxil fumarate (TDF) 300mg tablet (Viread)
    - Can be crushed and dissolved in water – has bitter taste
  - Combination tablet:
    - Truvada (TDF 300mg + emtricitabine 200mg) tablet
    - Atripla (TDF 300mg + emtricitabine 200mg + efavirenz 600mg) tablet
    - Complera (TDF 300mg + emtricitabine 200mg + rilpivirine 25mg) tablet
    - Stribild ((TDF 300mg + emtricitabine 200mg + elvitegravir 150mg + cobicistat 150mg)

- TDF also active against hepatitis B virus
  - In pts w/ HIV and HBV co-infection, HBV may flare upon TDF discontinuation
Tenofovir Adverse Effects

GI: flatulence, nausea, diarrhea, abdominal discomfort/bloating
Emtricitabine (FTC)/Lamivudine (3TC)

- Very similar drugs – use one or the other (never both)
- Both FTC/3TC active against hepatitis B virus
  - In pts w/ HIV and HBV co-infection, HBV may flare upon FTC/3TC discontinuation
Emtricitabine (FTC)/Lamivudine (3TC)

- Emtricitabine dose = 200mg once daily
  - FTC only available in Canada as part of combination pills
    - Truvada, Atripla, Complera, Stribild
    - 86% renal excretion; dose adjustments recommended if CrCl < 50mL/min
  - Well tolerated; potential for hyperpigmentation of hands/soles of feet in darker skinned individuals

- Lamivudine for HIV Tx
  - Available as 150mg and 300mg tablets or 10mg/mL oral liquid
  - Combination product with abacavir (Kivexa) taken once daily
    - Abacavir 600mg/lamivudine 300mg
  - Also included in Combivir and Trizivir combination products
  - Well tolerated;
    - Potential for headache (35%), nausea (33%), diarrhea (18%)

Lamivudine Product Monograph
Truvada Product monograph
Lamivudine (3TC) & Renal Dosing

- Dosing as per product monograph:
  - CrCl >50ml/min: 300mg OD or 150mg BID
  - CrCl 30-49ml/min: 150mg OD
  - CrCl 15-29ml/min: 150mg loading dose, then 100mg OD
  - CrCl 5-14ml/min: 150mg loading dose, then 50mg OD
  - CrCl <5mL/min: 50mg loading dose, then 25mg OD

- These renal dosing recommendations come from single-dose PK data obtained in a 1996 study with 16 HIV+ve pts

- Another study with 9 HIV+ve pts with end-stage renal disease tolerated 150mg 3TC OD, despite PK results suggesting certain PK values were ~5x higher than in pts with normal renal function

Lamivudine Product Monograph
Nephron. 2000; 86(4):553
Abacavir (ABC)

- **Dose**: 600mg once daily or 300mg BID

- **Available as**:
  - Abacavir (Ziagen) 300mg tablets or 20mg/mL suspension
  - Combination product with lamivudine (Kivexa) taken once daily
    - Abacavir 600mg/lamivudine 300mg

- **Preferred NRTI regimen for renal impairment**
Abacavir Hypersensitivity Reaction (HSR)

- Potentially life-threatening, multi-system reaction
- Non-specific symptoms: fever, rash, GI, malaise, respiratory issues
- Usually occurs within first 6 weeks after abacavir initiation (median time to onset = 11 days)

Hypersensitivity Related Symptoms Reported with ≥10% Frequency in Clinical Trials (n=206 Patients)
Abacavir Hypersensitivity Reaction (HSR)

- HLA-B*5701 screening
  - Very strong association between HLA-B*5701 presence and abacavir HSR
  - If positive, 40-50% chance of abacavir HSR
  - First clinically used genetic test to prevent drug toxicity

- More than 11,000 HLA-B*5701 tests performed since 2006 in Canada
  - 6.3% of these tests were positive

If HLA-B*5701 positive DO NOT initiate abacavir

- Although unlikely, still possible to have abacavir HSR if HLA-B*5701 negative

Abacavir and MI Risk

Literature re: ABC and MI Risk is controversial
Efavirenz (EFV)

- Approved EFV dose = 600mg once daily

- Available as:
  - Combination product (Atripla) taken once daily
    - Efavirenz 600mg + 300mg tenofovir disoproxil fumarate + 200mg emtricitabine
    - Efavirenz (Sustiva or generic) 600mg tablet
    - Efavirenz 200mg or 50mg capsules

- Administration:
  - Take AT BEDTIME to reduce CNS s/e
  - Take ON EMPTY STOMACH to limit s/e
    - High fat foods absorption by 50%
  - Swallow tablet/capsule whole
    - Efavirenz is insoluble in H₂O
    - Not recommended to split/crush Atripla/efavirenz tablets
    - Capsules can be opened & powder mixed in applesauce, but get hot “jalapeno” sensation. Can add grape jelly to mask taste
Efavirenz (EFV): Adverse Effects

- **CNS s/e**
  - Abnormal/vivid dreams, insomnia, dizziness, ↓’d concentration, somnolence, confusion, headache, mood/psychiatric changes
  - Incidence = 53% of EFV patients vs. 25% in control regimen group
  - Onset of CNS s/e can be w/in first couple days of EFV Tx
  - Severity usually ↓’s w/ 2-4 weeks of use, but symptoms can persist
  - Close monitoring/caution needed in pts w/ mental health illness

- **Rash (incidence = 26%)**
  - Usually occurs w/in 2 weeks of starting therapy (median onset = 11 days)
  - Most cases resolve w/in 1 month (median duration = 16 days) w/ continued EFV Tx
  - Antihistamines &/or topical corticosteroids may improve tolerability & hasten rash resolution
  - Severe rash (associated with blistering, moist desquamation, or ulceration) reported in 0.9% of efavirenz Tx’d patients
    - Discontinue Tx if severe rash occurs

- **Other**: N/V/D, increased LFTs, hyperlipidemia/hypertriglycerideridemia,

- ? teratogenic; not recommended in first trimester of pregnancy

Efavirenz Product Monograph, Micromedex Efavirenz Monograph
Rilpivirine (RPV)

- 2nd generation NNRTI available as:
  - 25mg tablet (Edurant) taken once daily
  - Combination tablet (Complera) taken once daily:
    - 25mg RPV + 300mg tenofovir disoproxil fumarate + 200mg emtricitabine

- Take RPV with food

<table>
<thead>
<tr>
<th>Table: Meal Options Comprising 500-600 kcal</th>
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<tbody>
<tr>
<td>- 2 slices of whole wheat toast with peanut butter, fresh fruit, and 1 cup orange juice (509 calories)</td>
</tr>
<tr>
<td>- 2 eggs, 2 strips of bacon, and 2 slices of wheat toast with butter (520 calories)</td>
</tr>
<tr>
<td>- 2 toasted breakfast pastries, yogurt, and 1 cup of juice (596 calories)</td>
</tr>
<tr>
<td>- Plain bagel with 2 tbsp cream cheese, yogurt, and a banana (569 calories)</td>
</tr>
<tr>
<td>- Roast beef sandwich on a hard roll with mayonnaise and cheese (582 calories)</td>
</tr>
<tr>
<td>- 2 slices of cheese pizza and 1 can of regular soda (550 calories)</td>
</tr>
<tr>
<td>- Peanut butter and jelly sandwich on wheat bread, a banana, and 1 cup skim milk (562 calories)</td>
</tr>
<tr>
<td>- Veggie burger on a bun with tomato soup and a side salad (500 calories)</td>
</tr>
<tr>
<td>- Grilled chicken Caesar salad (521 calories)</td>
</tr>
<tr>
<td>- 2 cups of spaghetti with marinara sauce and 1 slice of bread (514 calories)</td>
</tr>
<tr>
<td>- Salmon with rice and fresh vegetables (596 calories)</td>
</tr>
<tr>
<td>- Tofu and vegetable stir-fry with brown rice and a side salad (527 calories)</td>
</tr>
</tbody>
</table>

- 2012 study suggesting Complera is effective with a light meal (390 kcal)

Rilpivirine Product Monograph

In phase III studies (ECHO and THRIVE), virologic response to RPV suboptimal in pts w/ baseline VL > 100,000 copies/mL

RPV requires acidic gastric environment for absorption
- PPIs contraindicated with RPV
- Must separate antacids and H2RAs from RPV administration

Well tolerated; less risk of CNS s/e, rash, and impact on lipids than efavirenz
In healthy subjects, rilpivirine 25mg daily was not associated with a statistically or clinically relevant effect on QTc interval, but rilpivirine in healthy individuals has been associated with QT interval prolongation at doses of 75 mg and 300 mg daily.

In ARV naïve HIV+ve patients receiving rilpivirine 25 mg daily in phase III clinical trials (which excluded pts with high risk factors for proarrhythmia) the mean QTc interval increased gradually over 48 weeks and remained stable through week 96.
Protease Inhibitor Class Side Effects

- Gastrointestinal
  - Nausea
  - Vomiting
  - Diarrhea (RTV is major culprit)

- Metabolic changes (Least impact = atazanavir)
  - Hyperlipidemia
  - Insulin resistance

- Fat re-distribution (lipodystrophy)
Atazanavir (ATV)

- **Standard Dosing:**
  - ATV 300mg once daily/ritonavir 100mg once daily
    - Note: ODB covers ATV 150mg capsules x 2 (not 300mg capsules)
  - ATV 400mg once daily if unboosted
    - Supplied as 200mg capsules x 2
    - Used when RTV use is not tolerated
      - *(ATV is more lipid friendly than other protease inhibitors)*
      - Not recommended if concurrent tenofovir use
  - Taken with food to enhance bioavailability & ↓ PK variability
  - Low gastric pH required for absorption (DDIs with acid reducing agents)
  - ATV is major CYP 3A4 substrate; ATV inhibits CYP 3A4 & UGT 1A1
  - Possible s/e of kidney stones
In controlled clinical trials, rash (all grades, regardless of causality) occurred in approximately 20% of patients treated with ATV.

- Median time to onset of rash in clinical studies was 7.3 weeks;
- Median duration of rash was 1.4 weeks.
- Rashes were generally mild-to-moderate maculopapular skin eruptions.
Unique Mechanism Of Action For ATV:
- Under normal circumstances, unconjugated bilirubin is converted to conjugated bilirubin via the UGT 1A1 enzyme.
- ATV, however, inhibits UGT 1A1 to cause unconjugated hyperbilirubinemia
Indirect (unconjugated) hyperbilirubinemia

- Usually benign; elevation in indirect bilirubin is reversible & independent of liver toxicity
- Unless clinical signs of jaundice or scleral icterus observed, ATV induced hyperbilirubinemia does not require management

Product Monograph:
- Incidence of ↑‘d bilirubin levels ~ 35-49%;
- Incidence of jaundice ~13% reported within a few days to a few months after Tx initiation w/ ATV Tx discontinuation in <1%
- No long-term safety data are available for patients experiencing persistent elevations in total bilirubin >5× ULN

*Indirect hyperbilirubinemia useful as surrogate marker for ATV adherence*
Darunavir (DRV)

- High genetic barrier to resistance
- 2 Dosing Regimens:
  - Darunavir 800mg/ritonavir 100mg once daily
  - Darunavir 600mg/ritonavir 100mg BID (for Tx experienced patients with at least 1 of the 11 darunavir associated resistance mutations)
- Take with food to ensure maximal absorption
  - 30% bioavailability ↑ when taken w/ food
- Can crush DRV tablets if needed; liquid DRV formulation is coming soon
- Can be taken with H2RAs and PPIs
- Drug interactions similar to other protease inhibitors
During the clinical development program (n=3063), severe skin reactions reported in 0.4% of patients
  - May be accompanied by fever and/or ↑'d transaminases

Rash of all grades occurred in 10.3% of patients treated with DRV/r
  - Rash was mostly mild-to-moderate, often occurring within the 1st 4 weeks of Tx and resolving with continued dosing
  - Discontinuation rate due to rash was 0.5%
Darunavir (DRV) & Sulfonamide Allergy

- DRV contains a sulfonamide moiety
- As per DRV Product Monograph:
  - “use with caution in patients with a known sulfonamide allergy”
  - Potential cross-sensitivity b/w sulfonamide class drugs & DRV is unknown
  - In clinical studies with DRV/r, incidence and severity of rash was similar in patients w/ or w/o a Hx of sulfonamide allergy

  - Observational study (n=292) re: DRV induced skin rash in Tx-naïve pts
  - DRV rashes developed in 31 (11%) with median latency = 10 days (7-14 days in 93% of cases)
  - Incidence of DRV rash not significantly different between pts w/ & w/o a Hx of sulfonamide allergy (p=0.201)
  - To date, no clear clinical evidence to suggest DRV should be avoided in patients with Hx of sulfonamide allergy
Darunavir (DRV) & Hepatotoxicity

- May 2008 - Health Canada Warning re: DRV & risk of hepatotoxicity
- Hepatic injury has generally occurred in patients with:
  - advanced HIV disease taking multiple concomitant medications
  - hepatitis B or C co-infection
  - and/or developing immune reconstitution syndrome
- Drug-induced hepatitis reported in 0.5% of patients using DRV/r during clinical trials.
- DRV/r contraindicated in severe hepatic impairment (Child-Pugh Class C)
Raltegravir (RAL)

- 1st integrase inhibitor on the market
  - Low genetic barrier to resistance
  - Causes rapid viral decay
- Only approved dose = 400mg BID
- QDMRK Study:
  - 800mg RAL OD + TDF/FTC failed to meet non-inferiority criteria when compared to 400mg RAL BID + TDF/FTC
  - 83% of 800mg OD group achieved VL < 50 copies/mL vs 89% of 400mg BID group (p=0.044)
- 800mg once daily after virologically suppressed?
  - Limited evidence
- 1200mg once daily currently under investigation as phase III trial
**Missed dose policy:**

- Take as soon as remembered, even if this means you take 2 of the raltegravir 400mg tablets close to the same time or at the exact same time.
- Better to “double-up” on the raltegravir 400mg dose rather than completely miss a dose, but this should be done very infrequently.
- After the missed dose has been taken, continue on with the regular raltegravir dosing schedule.
**Raltegravir (RAL)**

- **Take w/ or w/o food**
- **Metabolized via UGT 1A1 mediated glucuronidation pathway**
- **Minimal drug interactions**
  - RAL dose doubled with concurrent rifampin
  - Concurrent Ca++ use is fine
  - Mg/Al containing antacids not recommended concurrently w/ RAL, but if used separate administration by 2 hrs
  - Preferred option for concurrent chemotherapy
- **Well tolerated, minimal effect on lipids/metabolic complications but side effects can include:**
  - headache, nausea, insomnia, rash/hypersensitivity reactions (SJS/TEN reported), ↑ CK (risk of myopathy/rhabdomyolysis)
Elvitegravir (EVG)

- Considerable overlap in resistance profiles of RAL and EVG
- Elvitegravir = CYP 3A4 substrate
  - Boosted with cobicistat to achieve optimal elvitegravir levels
  - Limitation is that cobicistat introduces CYP 3A4 related drug interactions
  - Separate by at least 2 hrs from antacids containing Al, Mg, or Ca
- Currently only available commercially as part of Stribild
  - Elvitegravir 150mg/cobicistat 150mg/tenofovir disoproxil fumarate 300mg/emtricitabine 200mg
  - Taken once daily
  - Recommended to take w/ food to achieve maximal EVG levels, but efficacious EVG levels can be achieved in fasted state
- Common side effects: nausea, diarrhea, headache
Stribild should only be started if baseline CrCl is > 70mL/min

What if ↑ SCr and ↓ CrCl are observed in patient taking Stribild?
- 2 processes to consider: benign ↑ SCr by inhibition of proximal tubular creatinine secretion by cobicistat vs. genuine nephrotoxicity 2° to TDF
- Suggested management:
  - Based on phase III studies, SCr change from baseline of 35umol/L is the threshold to discriminate b/w these 2 processes
  - If SCr increases > 35umol/L, work-up for genuine TDF related nephrotoxicity needed

Stribild should be D/C’d if actual CrCl < 50mL/min b/c Stribild is a fixed dose combination tablet and this doesn’t allow for appropriate renal dose adjustment

Stribild Product Monograph
German et al. J Acquir Immune Defic Syndr. 2012; 61(1); 32-40
Currently only commercially available as single entity product (Tivicay)
- Co-formulation with Kivexa coming soon = the next one pill once daily regimen

2 DTG dosing regimens:
- 50mg OD (Tx naïve; integrase inhibitor naïve)
- 50mg BID (in setting of integrase inhibitor resistance or select DDI cases, ie. concurrent efavirenz or rifampin use)

1° metabolized by glucuronidation via UGT 1A1 (minor oxidation via CYP 3A4)

Drug Interactions to note:
- Etravirine not recommended with DTG **UNLESS** co-administration w/ ritonavir boosted atazanavir, darunavir, or lopinavir
- Polyvalent cation containing drugs (ie. Mg, Al, Fe, or Ca) can ↓ DTG levels via binding interference
  - Take DTG 2 hrs before or 6 hrs after polyvalent cation containing meds
  - If taken w/ food, DTG may be taken at same time as Ca or Fe supplements
Dolutegravir (DTG)

- Take w/ or w/o food anytime of day
- May crush DTG tablet if swallowing whole is not an option
- Side effects:
  - Diarrhea, headache, insomnia, nausea
  - DTG can falsely ↑ SCr and ↓ CrCl via inhibition of renal tubular creatinine secretion by inhibiting OCT2 (renal organic cation transporter)
    - ↑ in SCr occurred w/in 1st 4 wks of DTG Tx and remained stable through 48 wks
    - Mean change in SCr from baseline after 48 wks of DTG Tx was 10umol/L
  - Hypersensitivity Reactions
    - Reported with integrase inhibitors, including DTG
    - Characterized by: rash, constitutional findings, and sometimes organ dysfunction (ie. liver)
- Not yet covered by ODB
Drug Interactions
**Drug Interaction with ARVs: “General” PK Principles**

<table>
<thead>
<tr>
<th>NRTIs</th>
<th>IIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>• minimal drug interactions</td>
<td>• Minimal to no enzyme inhibition or induction</td>
</tr>
<tr>
<td>• No CYP involvement</td>
<td>• Very few drug interactions</td>
</tr>
<tr>
<td></td>
<td>• Exception: elvitegravir/cobicistat (CYP3A, CYP2D6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NNRTIs</th>
<th>PIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>• CYP 3A4 inducer</td>
<td>• CYP3A4 inhibitor</td>
</tr>
<tr>
<td>• EFV,NVP&gt;ETR&gt;RPV</td>
<td>• RTV&gt;LPV/r&gt;DRV/r&gt;ATV/r&gt;ATV</td>
</tr>
<tr>
<td>• EFV may act as CYP3A4 inhibitor</td>
<td>• May inhibit other CYP enzymes: 2C19,2C9,2D6,1A2,2B6</td>
</tr>
<tr>
<td></td>
<td>• RTV (CYP3A&gt;2D6&gt;2C9&gt;2C19&gt;2A6&gt;2E1)</td>
</tr>
<tr>
<td></td>
<td>• RTV may act as inducer as well</td>
</tr>
</tbody>
</table>
Drugs that have a high potential for drug interactions in HIV patients

- Statins (esp. simvastatin, lovastatin)
- Anticonvulsants
- Methadone
- Anticoagulants (warfarin, rivaroxaban)
- Phosphodiesterase-5 inhibitors
- Oral contraceptives
- Antiarrhythmics
- Some oral benzodiazepines (ie. midazolam, triazolam)
- Antimycobacterials (rifampin)
Case Study #1

Mr. K

- 48 yo male; HIV+ve diagnosis 2006
- Medications:
  - Atripla 1 tab po HS
  - atorvastatin 40mg daily
  - ramipril 5mg daily

- Most recent lab results
  - CD4 420 cells/mm3
  - VL 620 copies/mL ➔ previous VL have all been <40 copies/mL

- New job working night shift; too “groggy” at work when he takes his Atripla
- Pt is used to taking one pill once a day and does not want to increase his pill burden
- Genotyping completed ➔ no drug resistance identified

- New RX: COMPLERA 1 TAB PO DAILY

- Mr. K comes to the pharmacy with his new ARV RX as well as an RX from his GP for pantoprazole 40mg daily for some recent GERD symptoms.
- Are there any concerns?
Drug Information for Healthcare Professionals

Drug Interaction Tables
Antiretroviral Interactions with Chemotherapy Regimens
Pharmacologic Properties of Antiretrovirals
Pharmacologic Properties of Hepatitis C Antivirals
Additional Information for Pharmacists and Physicians
Medication Fact Sheets for Patients
Reimbursement Information

News
We are very proud to announce that www.hivclinic.ca has recently received awards from two prestigious Canadian pharmacy organizations for excellence in pharmacy practice. We are honoured and humbled to be recognized by our colleagues and peers. Thank you!
### Antiretroviral Interactions

- CCR5 Inhibitors
- CCR5 Inhibitors (old: aplaviroc, vicriviroc)
- Integrase Inhibitors
- Nucleoside Reverse Transcriptase Inhibitors
- Non-nucleoside Reverse Transcriptase Inhibitors
- Protease Inhibitors
- Protease Inhibitors - Secondary agents (amprenavir, indinavir, nelfinavir, soft-gel saquinavir)
- Tenofovir

### Interactions with Other Drug Classes

- Acid-Reducing Agents
- Anticonvulsants
- Antihyperglycemics
- Antihypertensives
- Antimalarials
- Antineoplastic Agents (see also "Antiretroviral Interactions with Chemotherapy Regimens")
- Antiplatelet Agents and Novel Oral Anticoagulants

### Includes updates from:

- 20th International AIDS Conference, Melbourne, Australia, July 20-25, 2014
- 15th International Workshop on Clinical Pharmacology of HIV and Hepatitis Therapy, May 19-21, 2014, Washington, DC
- Conference on Retroviruses and Opportunistic Infections (CROI), March 3-6, 2014, Boston, MA
- 64th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD), November 1-5, 2013, Washington DC
- 14th European AIDS Conference (EACS), October 16-19th, 2013, Brussels
- 53rd International Conference on Antimicrobial Agents and Chemotherapy (ICAAC), September 10-13, 2013, Denver, CO
### Interactions between Acid-Reducing Agents and Antiretrovirals

<table>
<thead>
<tr>
<th>NNRTIs</th>
<th><strong>Antacids, Vitamins, etc.</strong></th>
<th><strong>H2 Antagonists (H2RA)</strong></th>
<th><strong>Proton Pump Inhibitors (PPIs)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Rilpivirine</td>
<td>Administer antacids at least 2 hours before or at least 4 hours after rilpivirine.</td>
<td>Rilpivirine AUC ↓ 76% with famotidine 40 mg. Rilpivirine should be separated at least 4 hours before or 12 hours following famotidine.</td>
<td>37% ↓ Cmin of rilpivirine with omeprazole 20 mg. <strong>Rilpivirine is contraindicated with PPIs.</strong></td>
</tr>
</tbody>
</table>
Drug Interaction: Acid Reducers and Rilpivirine

- Rilpivirine exposure reduced by 40%
- Combination of RPV and PPIs is contraindicated
- Negative effect of H2-blockers can be avoided if administered 12h before or 4hr after RPV

### Recommendations: Administration of ARVs with Acid Reducers

<table>
<thead>
<tr>
<th>ANTACIDS</th>
<th>Interaction</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atazanavir, ATV/r</td>
<td>⇣ATV</td>
<td>Give ATV,TPV at least 2hr before or 1hr after</td>
</tr>
<tr>
<td>Rilpivirine</td>
<td>⇣RPV</td>
<td>Give antacids at least 2hr before or 4hr after</td>
</tr>
<tr>
<td>Elvitegravir/cobicistat</td>
<td>EVG 40-50%</td>
<td>Separate Striibl and antacid by ≥ 2 hrs</td>
</tr>
<tr>
<td></td>
<td>15-20% if given within 2hrs</td>
<td></td>
</tr>
<tr>
<td>Dolutegravir</td>
<td>DTG AUC 74%; DTG AUC 26% if given 2 hrs before</td>
<td>Give DTG at least 2 hrs before or ≥ 6 hrs after</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>AL-Mg Hydroxide: RAL Cmin 54-63%</td>
<td>Separate Al-Mg hydroxide antacid by &gt; 2hrs</td>
</tr>
<tr>
<td></td>
<td>CaCo3: Cmin 32%</td>
<td>No dosing separation required for CaCo3 antacid</td>
</tr>
</tbody>
</table>

## Recommendations: Administration of ARVs with Acid Reducers

<table>
<thead>
<tr>
<th>H2 Receptor Antagonists</th>
<th>Proton Pump Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atazanavir</strong></td>
<td><strong>Not recommended</strong></td>
</tr>
<tr>
<td>ATV</td>
<td><strong>Give ATV at least 2hr before and at least 10hrs after the H2RA</strong></td>
</tr>
<tr>
<td><strong>Atazanavir/r</strong></td>
<td><strong>Give ATV/r simultaneously with and/or at least 10hrs after</strong></td>
</tr>
<tr>
<td><strong>Rilpivirine</strong></td>
<td><strong>Give H2RA at least 12hr before or 4hr after</strong></td>
</tr>
</tbody>
</table>

### H2 Receptor Antagonists

- **Atazanavir**: Give ATV at least 2hr before and at least 10hrs after the H2RA.
- **Atazanavir/r**: Give ATV/r simultaneously with and/or at least 10hrs after.
- **Rilpivirine**: Give H2RA at least 12hr before or 4hr after.

### Proton Pump Inhibitors

- **Atazanavir**: Not recommended.
- **Atazanavir/r**: Give PPIs at least 12hrs before ATV/r. Do not exceed omeprazole 20mg or equivalent.
- **Rilpivirine**: RPV AUC ↓40%, Cmin ↓33%. Contraindicated.

OPTIONS FOR MR. K

- **Continue Complera®**
  - d/c pantoprazole
  - Start ranitidine 300mg daily and take Complera 4hrs before or 12hr after
  - Use antacid prn and take Complera 2hrs before or 4hrs after

- **Switch Complera®**
  - Stribild
  - Discuss a multiple pill regimen
Case Study #2

Miss D

• 28 yo HIV+ve female; diagnosed 2 years ago with pregnancy
• 3 children; all HIV-ve
• Most recent lab values:
  CD4 620 (28%), VL <40 copies/mL

• Medications:
  • Truvada 1 tablet daily
  • Darunavir 800mg daily
  • Ritonavir 100mg daily
  • Ferrous gluconate 300mg daily

• She is requesting a Rx for birth control. What do you suggest?
Interactions with Other Drug Classes

- Acid-Reducing Agents
- Anticonvulsants
- Antihyperglycemics
- Antihypertensives
- Antimalarials
- Antineoplastic Agents (see also "Antiretroviral Interactions with Chemotherapy Regimens")
- Antiplatelet Agents and Novel Oral Anticoagulants
- Azole Antifungals
- Hepatitis C Directly Acting Antivirals
- Antiretroviral Treatment Options for Patients on DAAs - Summary
- Lipid-lowering Drugs
- Methadone
- Narcotics
- Oral Contraceptives
- Osteoporosis Medications

Additional Information:


Understanding and Managing Drug Interactions in HIV Disease

Interactions between Antiretrovirals (ARVs) and Hormonal Contraceptives

This document consists of the following sections:
1. Combined Oral Contraceptives (COC)
2. Progesterone-Only Oral Contraceptive
3. Emergency Contraception Drug Interactions
4. Transdermal Contraceptives (e.g., Evra®)
5. Implantable Contraceptive (e.g., Implanon®)
6. Depo-medroxyprogesterone (DMPA, Depo-Provera®)
7. Levonorgestrel-releasing Intrauterine System (LNG-IUS) (e.g., Mirena®, Nova-T®)
8. Canadian Contraceptives Overview

1. ARV and Combined Oral Contraceptive (COC) Drug Interactions

<table>
<thead>
<tr>
<th>Drug</th>
<th>ARV Kinetic Characteristics</th>
<th>Interaction</th>
<th>Suggestion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleotide Reverse Transcriptase Inhibitor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenofovir (Viread®)</td>
<td>Minimal systemic metabolism. Not substrate of OATP</td>
<td>No effect on norgestimate (NGM)-estradiol (EE)</td>
<td>No specific action required.</td>
</tr>
</tbody>
</table>
# Drug Interactions: Combined Oral Contraceptives

<table>
<thead>
<tr>
<th>ARV</th>
<th>Interaction</th>
<th>Suggestion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atazanavir</td>
<td>ATV: EE AUC ↑48%, NE AUC ↑110%</td>
<td>ATV: Max 30ug EE</td>
</tr>
<tr>
<td></td>
<td>ATV/r: EE AUC ↓19%, NGM AUC ↑85%</td>
<td>ATV/r: Min 30ug EE</td>
</tr>
<tr>
<td>Darunavir/r</td>
<td>EE AUC ↓44%</td>
<td>Use alternate/additional methods</td>
</tr>
<tr>
<td></td>
<td>NE AUC ↓14%</td>
<td></td>
</tr>
<tr>
<td>Lopinavir/r</td>
<td>EE AUC ↓42%</td>
<td>Use alternate/additional methods</td>
</tr>
<tr>
<td></td>
<td>NE AUC ↓16%</td>
<td></td>
</tr>
<tr>
<td>Efavirenz</td>
<td>EE AUC ↑37%, NGM AUC ↓64%</td>
<td>Use alternate/additional methods</td>
</tr>
<tr>
<td></td>
<td>LNG AUC ↓83%</td>
<td>May require ↑dose of progesterone when used for emergency contraception</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>EE AUC ↓29%</td>
<td>Use alternate/additional methods</td>
</tr>
<tr>
<td></td>
<td>NE AUC ↓19%</td>
<td></td>
</tr>
<tr>
<td>Elvitegravir/Cobicistat</td>
<td>EE AUC ↓25%, 2-fold AUC/Cmax NGM-active metabolite</td>
<td>Weigh risks and benefits, consider alternative suggest min 30ug EE</td>
</tr>
</tbody>
</table>

No specific action required: raltegravir, dolutegravir, rilpivirine, etravirine, maraviroc

### Drug Interactions: Other hormonal contraceptives

<table>
<thead>
<tr>
<th>Depo-medroxyprogesterone Acetate (Depo-Provera®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Not studied with all ARVs</td>
</tr>
<tr>
<td>• EFV, NVP</td>
</tr>
<tr>
<td>• LPV/r – monitor AE</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Levonorgestrel-releasing intrauterine systems (Mirena®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• CDC: benefits outweigh risk</td>
</tr>
<tr>
<td>• MOA unrelated to LNG levels</td>
</tr>
<tr>
<td>• Study of 12 HIV +ve women, LNG ▲levels slightly, estradiol levels remained in the follicular-phase range. No pregnancies. No affect on CD4 or VL.¹</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Transdermal Contraceptives</th>
</tr>
</thead>
<tbody>
<tr>
<td>• EE AUC 45% with LPVr</td>
</tr>
<tr>
<td>• Use of alternative/additional methods</td>
</tr>
</tbody>
</table>

¹Heikinheimo O et al, Hum Reprod 2006; 21(11):2857-61
Summary

- COC and transdermal concentrations reduced by RTV-boosted PIs, EFV, NVP and EVG/cobi → **Use alternate method**
- COCs can be combined with RGV, ETR, RPV or MVC
- COC concentrations increased with unboosted PI (ATV)
- No significant interactions expected with DMPA or IUS however further studies required.
Suggestions for Miss D

- Stay on current ARV regimen:
  - Mirena®
  - Depo-Provera®

- Change ARV regimen (check genotype):
  - Complera
  - Raltegravir (BID dosing)
  - Etravirine
  - Dolutegravir (drug coverage)

- Miss D has one more question: Would milk thistle interact with her ARVs?
# Drug Interaction Charts

**Step 1** Choose one or more HIV drugs (these will be the columns and initially will be selected automatically for rows)

**Step 2** Choose one or more combination classes or select from an A-Z list of drugs

**Step 3** Choose one or more combination drugs and deselect any HIV drugs that are not required as rows

**Step 4** View results

---

**Generic Drugs**

- **NEW - Trade Names**

  **Protease Inhibitor**
  - Atazanavir
  - Darunavir
  - Fosamprenavir
  - Indinavir
  - Lopinavir
  - Nelfinavir
  - others

  **NNRTI**
  - Delavirdine
  - Efavirenz
  - Etravirine
  - Nevirapine
  - Rilpivirine

  **NRTI**
  - Abacavir
  - Didanosine (ddI)
  - Emtricitabine (FTC)
  - Lamivudine (3TC)
  - Stavudine (d4T)
  - Tenofovir

  **Entry and Integrase Inhibitors**
  - Dolutegravir
  - Elvitegravir/cobicistat
  - Maraviroc
  - Raltegravir

---

**HIV Drug look-up chart**

```
Search Generic Drugs: [ ] [ ] [ ]
[Select]
```
<table>
<thead>
<tr>
<th>Herbals/Supplements/Vitamins</th>
<th>Atazanavir</th>
<th>Darunavir</th>
<th>Ritonavir</th>
<th>Efavirenz</th>
<th>Etravirine</th>
<th>Elvitegravir/cobicistat</th>
<th>Raltegravir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echinacea</td>
<td></td>
<td>□</td>
<td></td>
<td>□</td>
<td>□</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Garlic</td>
<td></td>
<td></td>
<td>□</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ginkgo biloba</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>□</td>
<td></td>
</tr>
<tr>
<td>Grapefruit juice</td>
<td></td>
<td></td>
<td></td>
<td>□</td>
<td></td>
<td>□</td>
<td></td>
</tr>
<tr>
<td>Milk thistle</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>□</td>
<td></td>
</tr>
<tr>
<td>Seville orange juice</td>
<td></td>
<td></td>
<td></td>
<td>□</td>
<td></td>
<td>□</td>
<td></td>
</tr>
<tr>
<td>St John’s Wort</td>
<td></td>
<td>□</td>
<td>□</td>
<td>□</td>
<td></td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Valerian</td>
<td></td>
<td>□</td>
<td>□</td>
<td>□</td>
<td></td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

**Description**

The effect of echinacea on CYP activity was assessed by use of a number of CYP probe drugs (caffeine for CYP1A2; tolbutamide for CYP2C9; dextromethorphan for CYP2D6 and midazolam for both hepatic and intestinal CYP3A) in a study in 12 healthy volunteers. The data demonstrated that echinacea caused inhibition of CYP1A2 and intestinal CYP3A activity and induction of hepatic CYP3A activity. The authors indicate that for CYP3A substrates (such as protease inhibitors), the type of drug interaction observed with echinacea will be dependent on the relative extraction of the drugs at hepatic and intestinal sites and will not be readily predicted. Certainly echinacea could contribute to inter-patient variability in protease inhibitor levels.


**Summary**

Coadministration has not been studied and it is difficult to predict interactions with garlic. Garlic has been shown to inhibit CYP2C9, 2C19, 3A4 in vitro but there are inconsistencies in the literature regarding the ability of garlic to modulate CYP activity in vivo (probably arising due to variations in the amount of garlic components used in different studies). Caution should be used when using garlic. Monitor darunavir plasma concentrations.

**Summary**

A case report suggests that Gingko biloba may lower efavirenz plasma levels. Plasma samples from a patient who started taking Gingko biloba showed decreasing efavirenz concentrations, which coincided with an increasing viral load.

**Description**

A case report describes a possible interaction with efavirenz and *Gingko biloba*. The patient had been on an antiretroviral regimen of tenofovir/emtricitabine and efavirenz for two years and had achieved an undetectable viral load. However, virological failure developed and upon questioning it was found that the patient had been taking Gingko biloba for several months. Efavirenz concentrations were determined in stored plasma samples and showed decreasing concentrations which coincided with increasing viral load. The patient was successfully switched to alternative antiretrovirals. Although the exact mechanism of the interaction remains unresolved, the authors propose that Gingko biloba extract (principally the terpenoids) may lower efavirenz plasma levels by the induction of CYP3A4 and P-gp.

Mr. B

63yo HIV+ve male with COPD and depression

Medications:
- Truvada (emtricitabine 200mg/tenofovir 300mg) one tab once daily
- Atazanavir 300mg once daily
- Ritonavir 100mg once daily
- Citalopram 20mg once daily
- Tiotropium 18mcg inhaled once daily
- Salbutamol 100mcg 1 puff Q4H PRN
- Fluticasone 125mcg inhaler I puff BID
- Formoterol 12mcg inhaled BID

What is the drug therapy problem of concern?
An interaction between fluticasone and ritonavir is well documented in the literature.

- Due to the risk of adverse effects, co-administration of fluticasone with ritonavir should be avoided.

This interaction has resulted in:

- Steroid accumulation
- Cushing’s syndrome
- Adrenal suppression

Fluticasone + Ritonavir

The average onset of Cushingoid features in the adult case reports was about 2.75 months (range 2 weeks to 6 months)

Why Fluticasone?

- Major CYP 3A4 substrate

- Compared to other inhaled/intranasal corticosteroids, fluticasone:
  - has a longer half-life (10.5 hours)
  - is more lipophilic
  - has been shown to have the most suppressive effect on the hypothalamic-pituitary-adrenal axis of the inhaled corticosteroids

Budesonide & Ritonavir

- Budesonide is also a major CYP 3A4 substrate

- Budesonide previously thought to be associated with lower risk of Cushing’s syndrome

- 5 case reports have demonstrated that both inhaled and oral budesonide can cause Cushing's syndrome in patients taking ritonavir.

- Jan 2013 FDA Labeling Update for Kaletra (lopinavir/ritonavir):
  - Concurrent use with systemic, inhaled, or intranasal budesonide not recommended

Beclomethasone dipropionate is preferred inhaled/intranasal option for patients using ritonavir

- At this point in time, beclomethasone’s metabolism is not well described in the literature.

- A study by Boyd et al. suggests the use of beclomethasone with ritonavir boosted PIs is relatively safe and not likely to cause systemic corticosteroid-associated adverse effects.

- Another study confirmed co-administration of inhaled beclomethasone with either darunavir/ritonavir or ritonavir alone 100 mg BID did not result in significant adrenal suppression.
If a patient taking a ritonavir (or cobicistat) based regimen is started on a corticosteroid, alert patient about:

- glucocorticoid excess (increased appetite, weight gain, fat redistribution including moon-like facies, acne, thinning of the skin, excessive bruising)
- adrenal insufficiency (chronic fatigue, muscle weakness, loss of appetite, weight loss)
- importance of promptly reporting any development of the aforementioned symptoms to a healthcare provider
HHS Updates re: HIV and ARVs
HIV Post-Exposure Prophylaxis (PEP)

- New occupational PEP guidelines out Sept 2013
- If HIV PEP drug therapy indicated, preferred regimen is:
  - Truvada once daily + Raltegravir 400mg BID x 28 days
- All PEP medication regimens should include 3 ARV drugs
  - In the past, 2 active drugs were sometimes recommended rather than 3 active drugs based on risk stratification → this is no longer the case
- Start PEP regimen ASAP; should be within 72 hours of HIV exposure
- All HHS Emergency Rooms have 3 day PEP kits with ARV educational handouts; pt is to go to drugstore to get remaining 25 days of ARVs
- McMaster Drugstore and Hamilton General Drugstore always have PEP ARVs in stock
- HHS supports Combivir 1 tab BID + Kaletra (200mg/50mg tabs) 2 tabs BID x 28 days as ARV regimen of choice in pregnancy should PEP be needed
Medical directive implemented Feb 18, 2014

If SIS Clinic MD is unavailable, SIS Clinic RPhs are authorized to:
- renew prescriptions for chronic condition, including antiretrovirals
- adapt, accept, transcribe and communicate physician medication orders for adult patients of the SIS Clinic

The SIS Clinic RPh may **NOT** renew a prescription for a narcotic or controlled drug

As per this medical directive procedure, Rx is to be dispensed under SIS Clinic MD’s name NOT the SIS Clinic RPh’s name

SIS Clinic RPh can also order HIV baseline and routine follow labwork as needed on behalf of SIS Clinic MD
Summary

- HIV Drug Therapy = at least 3 active ARVs
- All or nothing rule pertaining to ARV use
- Adherence = critical
- Today’s ARV regimens much better tolerated and simpler than in the past
- Potential for many DDIs; lots of resources for ARV DDI checking
Look forward to working together to help our SIS clients

“I don’t think that’s what the pharmacist meant when he said ‘Take for two days and skip a day.’”