# Drug Interactions with HIV and Psychiatric Medications

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# Guidelines

# DHHS: Changing Criteria for Initiating ART

| CD4+ Count, cells/mm$^3$ | 1998 | 2001 | 2006 | 2008 | 2009 | 2012/ 2013 |
|---|---|---|---|---|---|---|
| > 500 | Offer if VL > 20,000 | Offer if VL > 55,000 | Consider if VL ≥ 100,000 | Consider in certain groups | Consider | Treat |
| 350-500 | Offer if VL > 20,000 | Consider if VL > 55,000 | Consider if VL ≥ 100,000 | Consider in certain groups | Treat | Treat |
| 200-350 | Offer if VL > 20,000 | Offer, but controversy exists | Offer after discussion with patient | Treat | Treat | Treat |
| < 200 or symptomatic disease | Treat | Treat | Treat | Treat | Treat | Treat |

# **Initial** Regimens: Preferred

| | |
|---|---|
| **NNRTI based** | ▪Atripla (Efavirenz + tenofovir + emtricitabine) |
| **PI based** | ▪Reyataz + Norvir + Truvada (Atazanavir + ritonavir + tenofovir/emtricitabine)<br>▪Prezista + Norvir + Truvada (Darunavir + ritonavir + tenofovir/emtricitabine) |

**Atripla** 

→ **1/day**

**Reyataz/Norvir/Truvada**

→ **3/day**

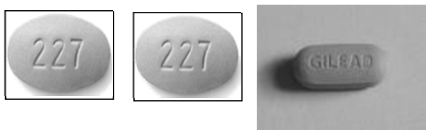
**Prezista/Norvir/Truvada**

→ **3/day**

## **Initial** Regimens: Preferred

| | |
|---|---|
| **II based** | ▪Isentress + Truvada (Raltegravir + tenofovir/emtricitabine<br>▪Tivicay + Truvada or Epzicom (Dolutegravir + tenofovir/emtricitabine OR abacavir/lamivudine<br>▪Stribild (Elvitegravir/cobicistat/tenofovir/ emtricitabine) |

**Isentress (BID)/Truvada**




→ **3/day**

**Tivicay/Truvada OR Epzicom**


**OR**


→ **2/day**

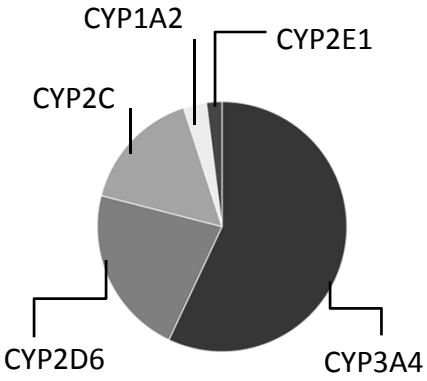
**Stribild**


→ **1/day**

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

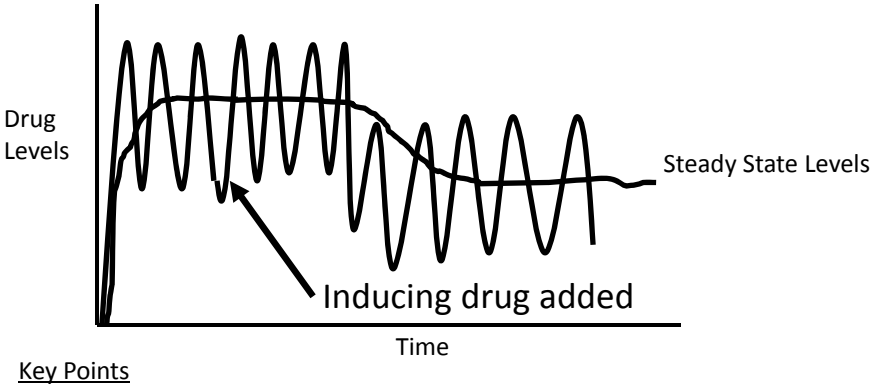



**Key points**

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

Adapted from Goodman and Gilman's The Pharmacological Basis of Therapeutics, 9th ed.

# CYP450 Induction



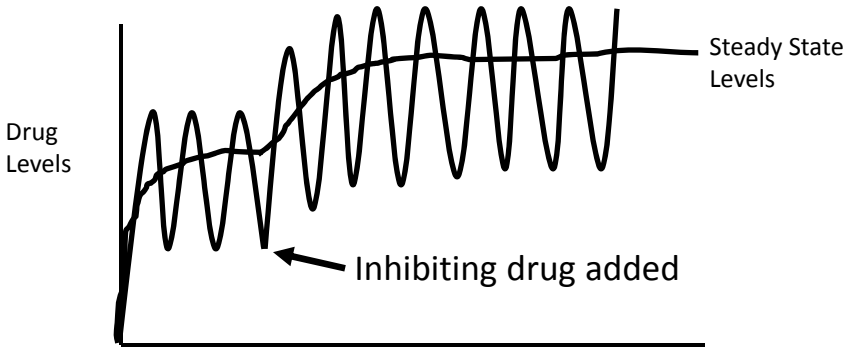

Key Points

- 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
- Fosphenytion
- 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 Lopinavir/rtv or Stribild to simvastatin

# Common CYP3A4 Inhibitors

- Clarithromycin
- Cobicistat
- Delavirdine
- Erythromycin
- Fluconazole
- Grapefruit Juice
- HCV Protease Inhibitors
- HIV Protease Inhibitors
- Itraconzaole
- Ritonavir

# Results of CYP450 inhibition Select Toxicities

| Drug | Potential Toxicity |
|---|---|
| Alfluzosin | Severe hypotension |
| Budesonide | Cushing's syndrome |
| Colchicine | Fever, diarrhea, paresthesias |
| Ergotamine derivatives | Ischemia, cyanosis, hypertension |
| Fluticasone | Cushing's Syndrome |
| Midazolam (oral), triazolam | CNS Depression |
| Quinidine | Cardiac arrhythmias |
| Sildenafil (and related drugs) | Syncope, hypotension |
| Statins (simvastatin, lovastatin) | Rhabdomyolysis |

## Contraindicated Medications with Protease Inhibitors, Cobicistat

| Class | Specific Medications |
|---|---|
| Cardiac Medications | Flecainide, propafenone, amiodarone, quinidine |
| Lipid Lowering Medications | Lovastatin, simvastatin |
| Antimycobacterial Medications | Rifampin, rifapentine |
| Gastrointestinal Medications | Cisapride |
| Neuroleptics | Pimozide |
| Psychotropics | Oral midazolam, triazolam |
| Ergotamine derivatives | DHE, ergotamine, ergonovine, etc |
| Herbal Therapy | St John's Wort |
| Other | Alfluzosin, salmeterol, sildenafil in PAH |

## Boosters – RTV, COBI

- Ritonavir
  - We know it, most major interactions worked out
  - Anything in a new drug label that mentions strong CYP3A4 inhibitors, think or ritonavir
  - Examples include ketoconazole, erythromycin, etc
  - Also inhibits PGP, CYP2D6, OAT transporters

# Boosters – RTV, COBI

- New booster in QUAD pill, Stribild®, co-formulated with elvitegravir, cobicistat, tenfovir and emtricitabine
- Contraindicated medications almost identical to RTV boosted PI regimens
- 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
- Note that many of the HIV – cobi interactions not entirely clear yet

Product Information, Stribild 2013

# 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

# Antidepressants

- Selective Serotonin Reuptake Inhibitors
  - Fluoxetine (Prozac®) & paroxetine (Paxil®, Pexeva®):
    - 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%)
  - Vilazodone (Viibryd®) – reduce dose to 20mg when used with HIV PIs or cobicistat

DHHS Guidelines, February 2013

# Antidepressants

- Tricyclic antidepressants
  - All boosted PIs and cobicistat expected to increase levels of TCAs
  - IE: desipramine levels increased 59% with ritonavir
  - Cobicistat (in Stribild) shown to increase desipramine levels 65%
  - Similar increases likely for amitriptylinr, imipramine, nortripyline
  - Monitor for anticholinergic side effects, EKG, TCA levels

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# Other Antidepressants

- SNRIs:
  - Mirtazapine (Remeron®) & duloxetine (Cymbalta®)
    - Generally well tolerated
  - Venlafaxine (Effexor®) and desvenlafaxine (Pristiq®)
    - PIs and Cobicistat may increase levels use caution
- Bupropion (Wellbutrin®, Zyban®)
  - AUC decreased 57% with lopinavir/rtv
  - AUC decreased 46% with tipranavir/rtv
- Trazodone (Deseryl®)
  - With ritonavir-boosted PIs and cobicistat, start low, titrate
- Avoid nefazodone, fluvoxamine

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# Other Antidepressants

- MAOIs
  - Avoid other antidepressants, mepridine, tramadol, sumatriptan, dextromethorhpen, linezolid
  - Other drugs may also be a problem
  - Beware of 14 day washout period prior to starting

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# 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)
  - **L**orazepam (Ativan®)
  - **O**xazepam (Serax®)
  - **T**emazepam (Restoril®)
- Use at lower doses & titrate with all PIs and cobicistat
  - Alprazolam, clonazepam, diazepam

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# Non-Benzodiazepine Sedative Hypnotics

- Zolpidem and zaleplon
  - Use lowest doses with PIs and cobicistat
  - Label changes for women, dose NTE 5mg zolpidem
- Eszopiclone
  - Use lowest dose, if at all, with PIs and cobicistat ketoconazole shown to more than double levels
- Buspirone levels likely to be increased by PIs and cobicistat

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# 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®), quetiapine (Seroquel®) clozapine (Clozaril®) iloperidone, lurasidone
  - Isolated case reports demonstrating toxicity with boosted PIs
  - Most are likely to be increased by protease inhibitors

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# Atypical Antipsychotic Metabolism

| Atypical antipsychotic | CYP450 metabolism |
|---|---|
| **Aripirazole** | 3A4, 2D6 |
| **Asenapine** | 1A2 |
| **Clozapine** | 3A4, 2D6, 1A2, 2C19 |
| **Iloperidone** | 3A4, 2D6 |
| **Lurasidone** | 3A4 |
| **Olanzapine** | 2D6, 1A2 |
| **Paliperidone** | No effect |
| **Quetiapine** | 3A4 |
| **Risperidone** | 2D6, 3A4 |
| **Ziprasidone** | 3A4 |

# HIV and Second Generation Antipsychotic Use

- Data from UCSD, retrospective, over 2200 patients
- Concomitant SGAs were frequent (12%) in this large, diverse cohort of ARV treated HIV+ individuals
- Psychiatric comorbidities were common among those taking SGAs
- Among ARV-treated HIV+s, those on concomitant SGAs had higher rates of diabetes mellitus and hypertriglyceridemia, and had elevated BMI and mean arterial blood pressure
- Just be cautious of additional contribution of newer antipsychotics to metabolic changes

Ferrara M, et al. AIDS 2012. Abstract MOPE097.

# Anticonvulsants and Stimulants

- In general with carbamazepine, phenobarbital, phenytoin, oxcarbazepine
  - Avoid with NNRTIs, PIs, cobicistat, elvitegravir
  - with maraviroc, need to increase dose to 600mg BID if used withOUT a CYP3A4 inhibitor
- Ritonavir boosted PIs may increase modafanil, methylphenidate, amphetamine, and dextroamphetamine levles

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# Narcotics

- Fentanyl – HIGH dose ritonavir increased fentanyl
  - Low dose patches to start, titrate slow, monitor closely
  - Caution regarding recreational use and bucal absorption
- Hydrocodone, tramadol – Potential to be increased with ritonavir via CYP2D6 inhibition
- Oxycodone and Lopinavir/rtv 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


Eur J Clin Pharmacol. August 2010, www.nynjaetc.org , DHHS Guidelines February 2013.

## Methadone and HIV Medications

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

## Methadone and HIV Medications

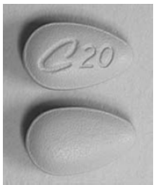
| HIV Medication | Pharmacokinetic Information and Clinical Implications |
|---|---|
| Atazanavir/ritonavir<br>Darunavir/ritonavir<br>Fosamprenavir/ritonavir | R methadone AUC decreased 16% to 18%; methadone withdrawal unlikely but possible; increase methadone dose as clinically indicated |
| Lopinavir/ritonavir | Methadone AUC decreased 25% to 53%; methadone withdrawal unlikely but possible; increase methadone dose as clinically indicated |
| Saquinavir/ritonavir | R methadone AUC decreased 19%; methadone withdrawal unlikely but possible; increase methadone dose as clinically indicated |
| Tipranavir/ritonavir | R methadone AUC decreased 48%; methadone withdrawal unlikely but possible; increase methadone dose as clinically indicated |

## Buprenorphine and HIV Medications

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

# 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 in crease with RTV 600mg BID not recommended with any boosted PI
- See DHHS Guidelines for PAH dosing





DHHS Guidelines March 2013.

# 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
- Ecinacea – 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

# Resources for You

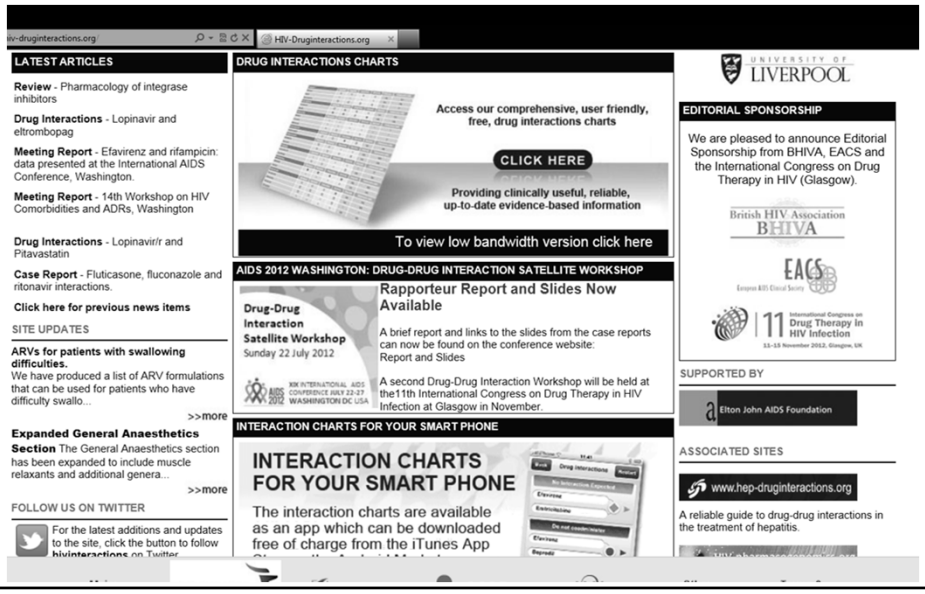
## Drug Interaction Questions

- Interaction has a clear answer, cut and dry PK data
- Interaction has an answer for similar drugs with similar properties where we can at least make comparisons
- Interaction has no answer, rely on trial and error to see
- Either way, try to give options, not answers

# Databases “Issues”

- Some over call interactions
  - Entire class versus individual medications
- Some miss case reports, so incomplete
- Always do a medline search
  - ie: warfarin and lactulose on lexicomp
- Stick to reputable HIV driven references for first step to screen for interactions

# www.hiv-druginteractions.org



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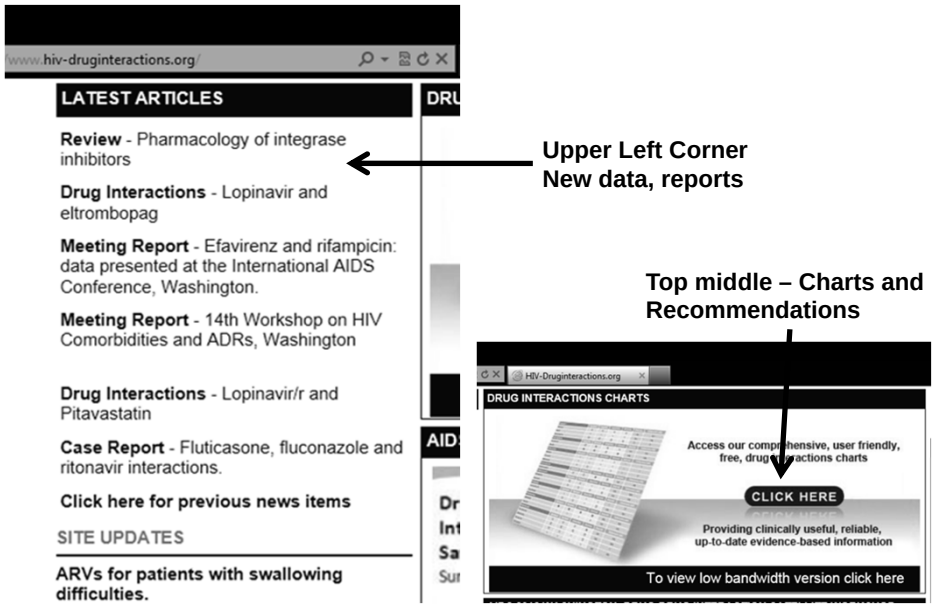
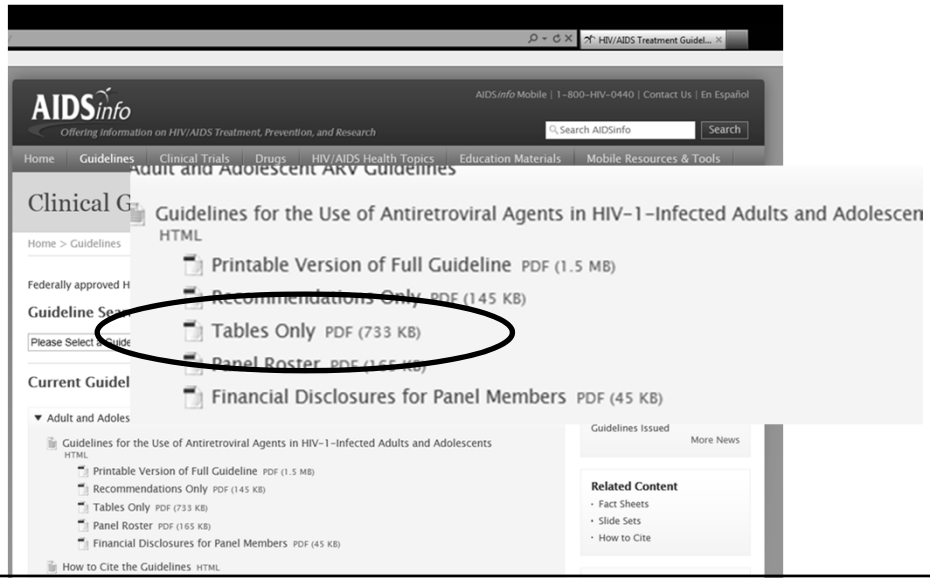
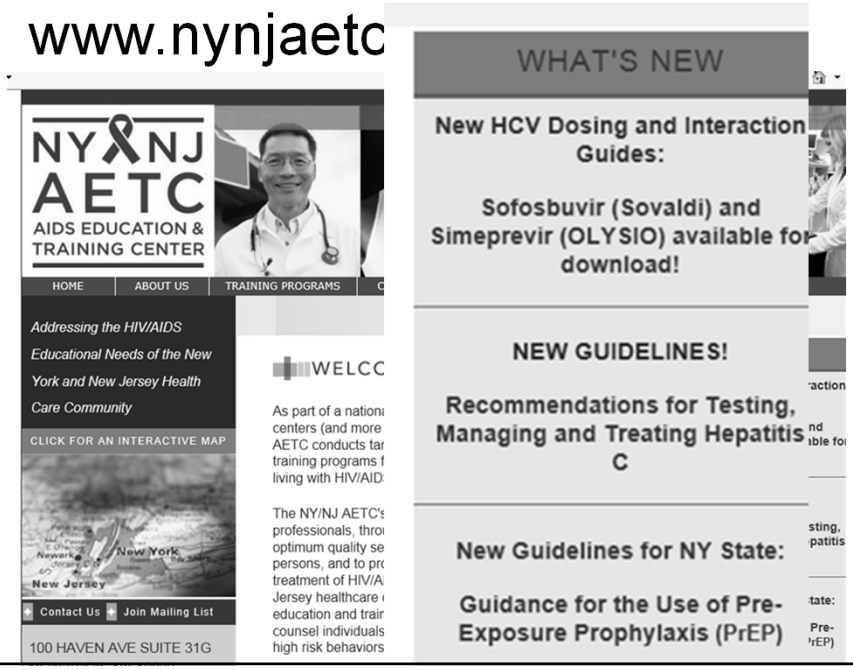


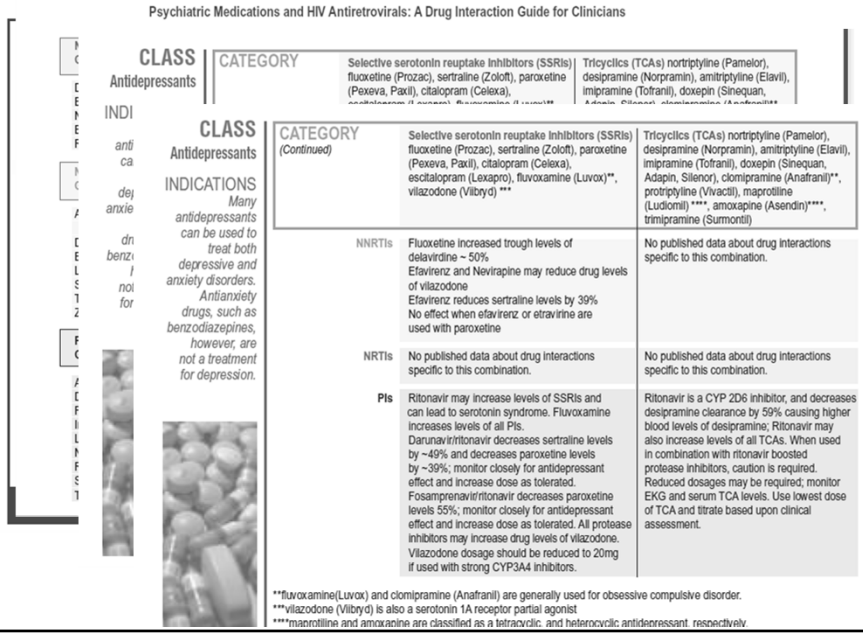

# http://aidsinfo.nih.gov/guidelines/



# www.nynjaetc




# NY/NJ AETC – www.nynjaetc.org



Psychiatric Medications and HIV Antiretrovirals: A Drug Interaction Guide for Clinicians

CLASS: Antidepressants

| CATEGORY | Selective serotonin reuptake inhibitors (SSRIs) fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Pexeva, Paxil), citalopram (Celexa), escitalopram (Lexapro), fluvoxamine (Luvox)**, vilazodone (Vilbryd) *** | Tricyclics (TCAs) nortriptyline (Pamelor), desipramine (Norpramin), amitriptyline (Elavil), imipramine (Tofranil), doxepin (Sinequan, Adapin, Silenor), clomipramine (Anafranil)**, protriptyline (Vivactil), maprotiline (Ludiomil) ***, amoxapine (Asendin)***, trimipramine (Surmontil) |
|---|---|---|
| NNRTIs | Fluoxetine increased trough levels of delavirdine ~ 50%<br>Efavirenz and Nevirapine may reduce drug levels of vilazodone<br>Efavirenz reduces sertraline levels by 39%<br>No effect when efavirenz or etravirine are used with paroxetine | No published data about drug interactions specific to this combination. |
| NRTIs | No published data about drug interactions specific to this combination. | No published data about drug interactions specific to this combination. |
| PIs | Ritonavir may increase levels of SSRIs and can lead to serotonin syndrome. Fluvoxamine increases levels of all PIs.<br>Darunavir/ritonavir decreases sertraline levels by ~49% and decreases paroxetine levels by ~39%; monitor closely for antidepressant effect and increase dose as tolerated.<br>Fosamprenavir/ritonavir decreases paroxetine levels 55%; monitor closely for antidepressant effect and increase dose as tolerated. All protease inhibitors may increase drug levels of vilazodone. Vilazodone dosage should be reduced to 20mg if used with strong CYP3A4 inhibitors. | Ritonavir is a CYP 2D6 inhibitor, and decreases desipramine clearance by 59% causing higher blood levels of desipramine; Ritonavir may also increase levels of all TCAs. When used in combination with ritonavir boosted protease inhibitors, caution is required. Reduced dosages may be required; monitor EKG and serum TCA levels. Use lowest dose of TCA and titrate based upon clinical assessment. |

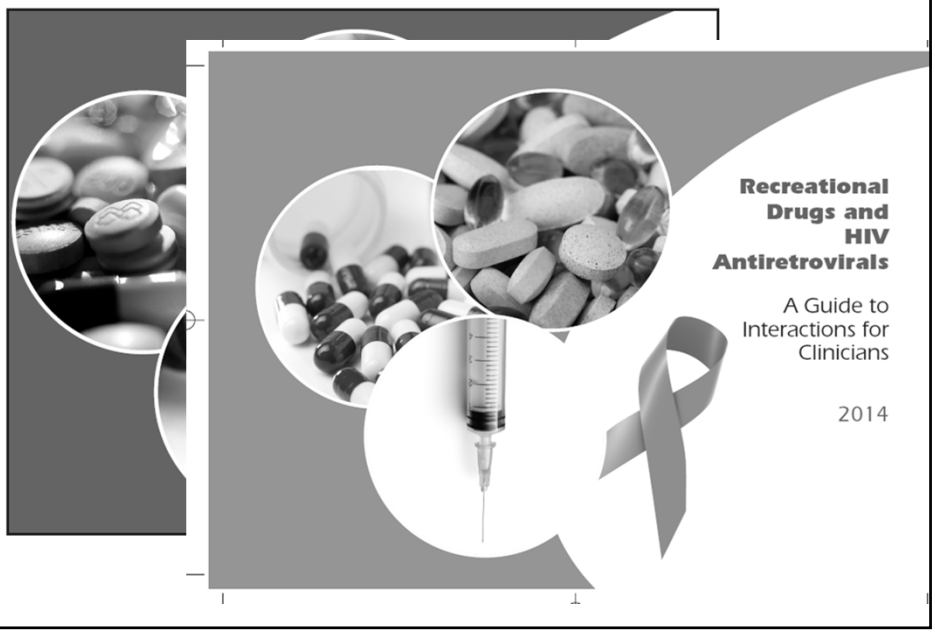
CLASS: Antidepressants

INDICATIONS: *Many antidepressants can be used to treat both depressive and anxiety disorders. Antianxiety drugs, such as benzodiazepines, however, are not a treatment for depression.*



**fluvoxamine(Luvox) and clomipramine (Anafranil) are generally used for obsessive compulsive disorder.
***vilazodone (Vilbryd) is also a serotonin 1A receptor partial agonist
****maprotiline and amoxapine are classified as a tetracyclic, and heterocyclic antidepressant, respectively.

## NY/NJ AETC – www.nynjaetc.org




## Questions