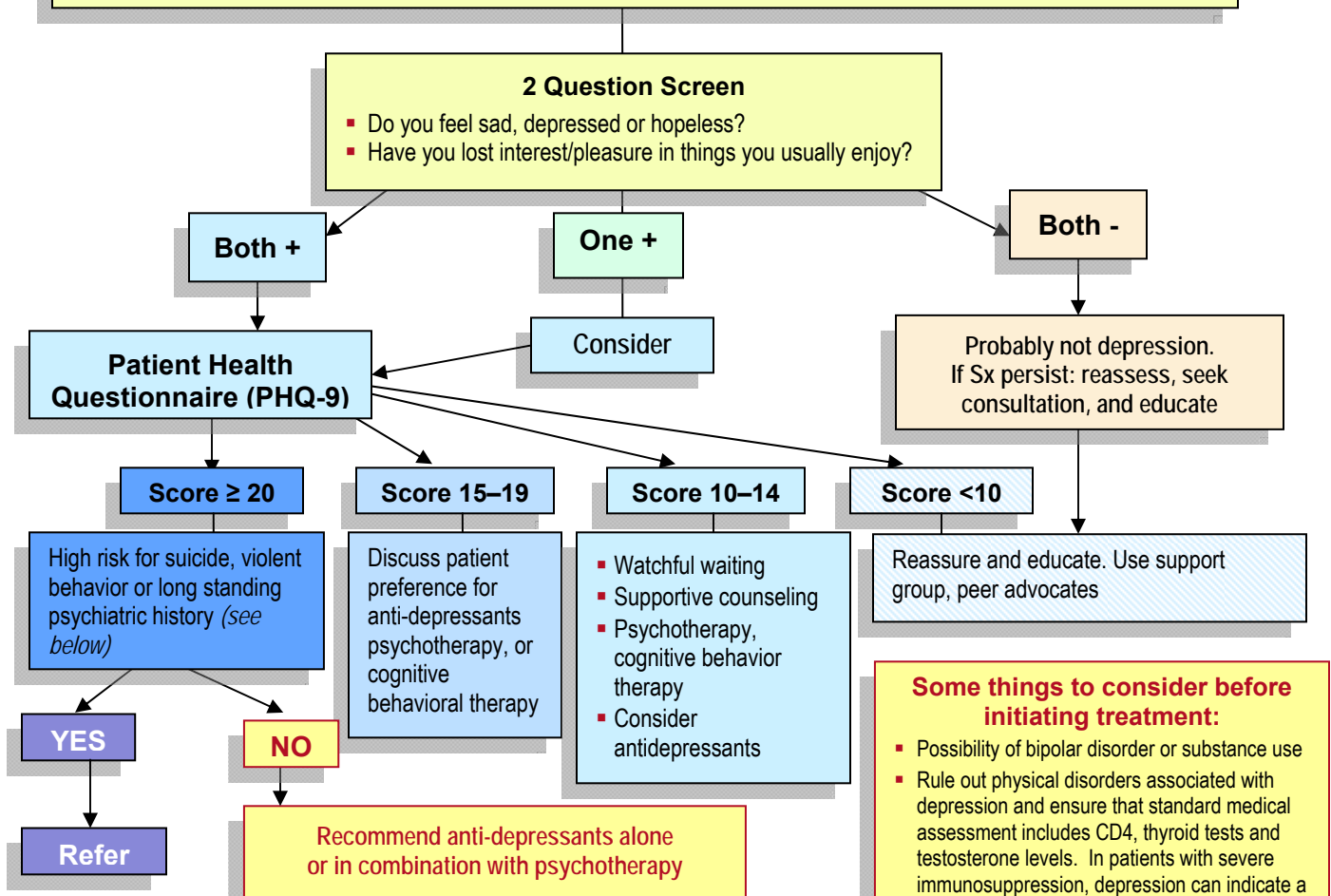


Depression Diagnostic Algorithm

Studies consistently show higher levels of depression in HIV-infected patients. Treating depression is associated with improved:

- Adherence
- Risk reduction
- Morbidity
- Mortality

Depression symptoms reported by family member or patient: sad mood, loss of pleasure or interest, low energy, tearfulness, restlessness, poor adherence to ARV medications, sleep problems (including early morning awakening or sleep continuity disturbance) talk of suicide, suicide plans, or giving things away.



Suicidality Screen:

- Patient or family reports that patient has contemplated, threatened, or attempted suicide. Look for self harm evidence.
 - If current attempt, determine specifics and potential lethality.
 - If no current attempt, ask patient
 - Have you felt that you would be better off dead or that you want to purposely hurt yourself?
 - Have you ever attempted suicide?
- If high risk, ensure constant observation and hospitalize if possible.
- Attend to medical sequelae of current attempt.
- Refer to Mental Health qualified provider.
- Institute general management and advise family – see <http://www.mentalneurologicalprimarycare.org>

Some things to consider before initiating treatment:

- Possibility of bipolar disorder or substance use
- Rule out physical disorders associated with depression and ensure that standard medical assessment includes CD4, thyroid tests and testosterone levels. In patients with severe immunosuppression, depression can indicate a new OI.
- If patient recently began efavirenz (EFV) assess if patient can tolerate waiting to see if symptoms spontaneously improve. If not, treat depression or consider ARV regimen change.
- Institute general management and advise family – see <http://www.mentalneurologicalprimarycare.org>

Selecting Anti-Depressant Medications for Patients with HIV/AIDS

- Consider side effect profiles as a means to treat other symptoms (eg, activating medications taken in the morning if the patient complains of low energy, medications that increase the appetite in patients with wasting syndrome, sedating medications taken at bedtime if the patient complains of sleep problems).
- Monitor patients closely after starting antidepressant medications; in some patients there is a risk of worsening depression, including suicidality, after initiation of therapy.
- Because of the potent inhibition of the microsomal cytochrome P450 isoenzymes by protease inhibitors (especially ritonavir), antidepressants used concomitantly with protease inhibitors should be started at low dosages and titrated cautiously to prevent antidepressant side effects/toxicity.
- Interactions between selective serotonin reuptake inhibitors (SSRIs) and HIV medications are fairly common. For patients who are starting antiretroviral medications (particularly protease inhibitors) and are on a stable antidepressant regimen, an empiric dosage reduction of antidepressant therapy should be considered, especially if the antidepressant dose is at the high end of the dose range and/or patient is having side effects of the antidepressant prior to starting antiretroviral therapy. Consultation among an HIV expert, psychiatrist, and clinical pharmacist can assist in developing an effective antidepressant and HIV regimen combination.
- **Therapeutic trial:** treatment for 4-6 weeks at therapeutic dosage. Medications should be continued for 6-9 months beyond the resolution of symptoms, because of significant risk of recurrence. After this time, treatment may be gradually tapered if so desired by the patient, with careful monitoring for recurrence of symptoms. Risk of recurrence is higher if first depressive episode is inadequately treated, or if the patient has had multiple depressive episodes.

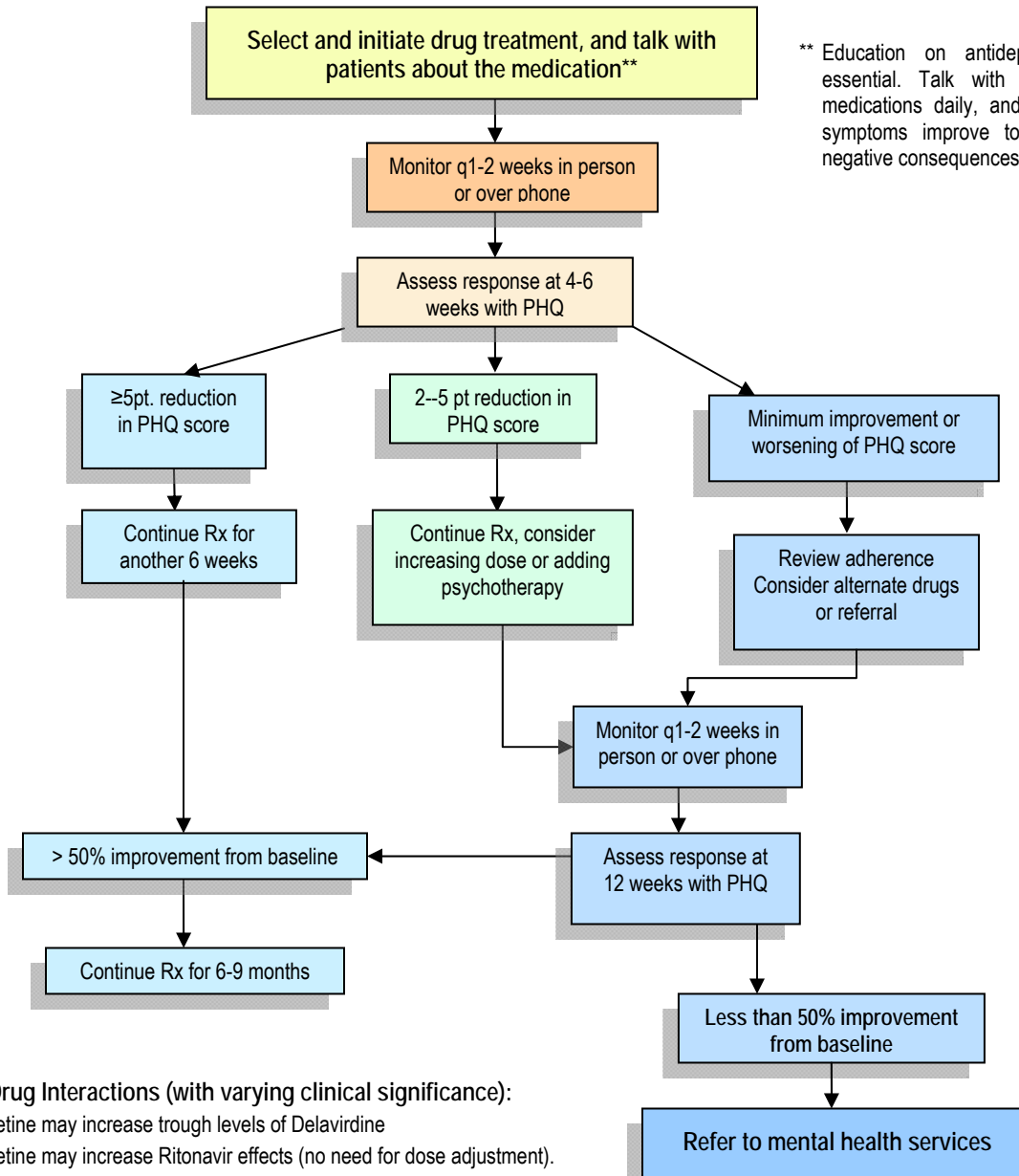
Adapted from: AETC Clinical Manual for Management of the HIV-Infected Adult, 2005 Edition, Chapter 7: Neuropsychiatry Disorders. Retrieved from, http://www.aidsetc.com/aetc/aetc?page=cm-702_depression

Commonly Used Antidepressant Medications

Drug Class	Generic name (Brand name)
Selective serotonin re-uptake inhibitors (SSRIs) First-line antidepressants	<ul style="list-style-type: none"> • Citalopram (Celexa) • Sertraline (Zoloft) • Fluoxetine (Prozac Sarafem) • Paroxetine (Paxil) • Escitalopram (Lexapro)
Novel antidepressants	<ul style="list-style-type: none"> • Bupropion (Wellbutrin) • Venlafaxine (Effexor) • Mirtazapine (Remeron)
Tricyclic antidepressants	<ul style="list-style-type: none"> • Nortriptyline (Aventyl, Pamelor) • Desipramine (Norpramin, Petrofrane) • Doxepin (Adapin, Sinequan) • Imipramine (Tofranil)
Psychostimulants	<ul style="list-style-type: none"> • Methylphenidate (Concerta, Metadate, Methylin, Ritalin) • Dextroamphetamine (Adderall)

Adapted from: Depression and Mania in Patients with HIV/AIDS, chapter in Mental Health Care for People with HIV Infection: HIV Clinical Guidelines for the Primary Care Practitioner. Updated February 2005. Developed by the New York State Department of Health AIDS Institute, Mental Health Guidelines Committee.

Depression Treatment Algorithm



** Education on antidepressant treatment is essential. Talk with patients about taking medications daily, and continuing even after symptoms improve to prevent relapse and negative consequences

Drug-Drug Interactions (with varying clinical significance):

- Fluoxetine may increase trough levels of Delavirdine
- Fluoxetine may increase Ritonavir effects (no need for dose adjustment).
- Ritonavir increases levels of fluoxetine, fluvoxamine, paroxetine and sertraline.
- Ritonavir may increase levels of desipramine, amitriptyline, doxepin, imipramine and nortriptyline (caution, use lower doses, monitor EKG and TCA levels)
- Efavirenz, nelfinavir and ritonavir may increase bupropion levels (mild risk of drug-induced seizures)
- Venlafaxine may decrease indinavir levels (clinical significance is unknown)
- Trazodone levels may increase with indinavir and other CYP3A4 inhibitors (ketoconazole, itraconazole): consider decreasing trazodone dose.

See **HIV/PSYCHOTROPIC MEDICATIONS INTERACTIONS** Table for Further Detail (pages 9-11)

Reference Tools for Providers

Depression recognition/assessment

- **The Depression Management Toolkit** (*The MacArthur Initiative on Depression and Primary Care*)
http://www.depression-primarycare.org/images/pdf/macarthur_toolkit.pdf
- **Suicidality in Patients with HIV/AIDS** (NY AIDS Institute Clinical Guidelines, "Mental Health Care for People With HIV Infection: HIV Clinical Guidelines for the Primary Care Practitioner")
<http://www.hivguidelines.org/GuideLine.aspx?pageID=261&guideLineID=84&vType=txt>
- **HIV and Suicide: Risk Assessment & Intervention.** Mountain Plains AETC, April 2007
[http://www.mpaetc.org/downloads/suicide_guide\(final_complete_web\).pdf](http://www.mpaetc.org/downloads/suicide_guide(final_complete_web).pdf)

Selecting and starting antidepressants

- **Depression and Mania in Patients with HIV/AIDS** (NY AIDS Institute Clinical Guidelines, "Mental Health Care for People With HIV Infection: HIV Clinical Guidelines for the Primary Care Practitioner")
<http://www.hivguidelines.org/GuideLine.aspx?pageID=261&guideLineID=39&vType=txt>
- **Mental Health Disorders** (HIV/AIDS Bureau, *A Guide to Primary Care of People with HIV/AIDS*)
<http://aidsetc.org/pdf/p02-et/et-30-25-01/et-30-25-PCARE-14.pdf>
- **Practice Guideline for the Treatment of Patients with HIV/AIDS** (American Psychiatric Association) <http://www.psych.org/AIDS/>

Maintaining patients on antidepressants

- **Guidelines: Interactions between HIV-Related Medications and Psychotropic Medications: Indications and Contraindications** (*NY AIDS Institute*)
<http://www.hivguidelines.org/GuideLine.aspx?pageID=261&guideLineID=62&vType=txt>
- **Psychiatric medications and HIV Antiretrovirals: A Pocket Guide to Interactions for Clinicians** <http://www.nynjaetc.org/productImages/Psychiatric%20Guide.pdf>
- **Tolerability Issues Affecting Adherence to Antidepressant Therapy** (Managing SSRI side effects, *University of Virginia monograph, CME credit*)
<http://www.healthsystem.virginia.edu/internet/cme/brochures/psych/uva-psych-dis-2-1-.pdf>

Patient education tools

- **Interactive patient education materials on depression in primary care**
http://www.depression-primarycare.org/clinicians/toolkits/materials/patient_edu/what_is_depression/
- **NIMH fact sheet on depression and HIV/AIDS**
<http://permanent.access.gpo.gov/lps37129/dephiv.pdf>

Patient Health Questionnaire—PHQ-9

Name: _____ Date of Birth : _____ Today's Date: _____

Fill in the boxes with pen or pencil to mark your answers.

A. Over the last 2 weeks, how often have you been bothered by any of the following problems?

	Not at all 0	Several days 1	More than half the days 2	Nearly every day 3
1. Little interest or pleasure in doing things	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. Feeling down, depressed, or hopeless	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. Trouble falling/staying asleep, sleeping too much	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. Feeling tired or having little energy	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. Poor appetite or overeating	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. Feeling bad about yourself – or that you are a failure or have let yourself or your family down.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7. Trouble concentrating on things, such as reading the newspaper or watching television.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. Moving or speaking so slowly that other people could have noticed. Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9. Thoughts that you would be better off dead or of hurting yourself in some way.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Total Score ____ = ____ + ____ + ____ + ____				

B. If you have been bothered by any of the 9 problems listed above, please answer the following:

How difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all

Somewhat Difficult

Very Difficult

Extremely Difficult

This health survey was adapted from the PRIME-MD® Patient Health Questionnaire © 1999, Pfizer Inc. Reproduced with permission. For research information, contact Dr. Robert L. Spitzer at rls8@columbia.edu.

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Patient Health Questionnaire—PHQ-9 Scoring Guidelines

PHQ-9 scores can be used to suggest depressive syndromes, plan, and monitor treatment. To score the instrument, tally each response by the number value under the answer headings. Add the numbers together to total the score on the bottom of the questionnaire. Interpret the score by using the guide below:

Guide for Interpreting PHQ-9 Question A (Items 1-9) Scores	
Score	Action
4 or less	Score suggests depression treatment may not be needed
5 to 14	Base clinical judgement about treatment on duration of symptoms and functional impairment
15 or more	Warrants treatment for depression using antidepressant, psychotherapy, and/or a combination treatment approach.

Major Depressive Syndrome is suggested if:

- Five or more of the nine items are checked as, at least, "More than half the days"
- Either item #1 or #2 is checked as, at least "More than half the days"

Other Depressive Syndrome is suggested if:

- Items #2, #3, or #4 are checked as, at least, "More than half the days"
- Either item #1 or #2 is checked as, at least "More than half the days"

Question B assesses functional health. The last two responses suggest impaired functionality. After treatment begins, functional status can be reassessed to see if patient is improving.

Interactions between HIV-Related Medications and Psychotropic Medications: Indications and Contraindications

Practitioners should refer to the full prescribing information of all medications their patients are taking. Doing so is particularly important when changes in mental status or the onset of psychiatric symptoms seem to be linked chronologically to changes in medication or dosage.

Most patients tolerate HIV-related medications without psychiatric or central nervous system side effects. However, when a change in mental status or the onset of psychiatric symptoms seems to be linked chronologically to changes in medications or dosage, it may be helpful to review the side effects described in the prescription literature.

Few psychiatric drugs are fully contraindicated for concomitant use with HIV-related medications. Consultation with a psychiatrist experienced in the treatment of HIV-infected patients is warranted when implementing combinations that suggest use with caution or when possible dose adjustment is recommended.

SSRIs and serotonin/norepinephrine reuptake inhibitors (SNRIs)

Fluoxetine (Prozac)	10-40 mg/day
Possible Positive Side Effects	
Possible Negative Side Effects	
rarely sedating, often energizing, no cardiovascular side effects, no anticholinergic effects, nonfatal in overdose	insomnia, agitation, nausea, headache, sexual dysfunction in men and women, long half-life

Paroxetine (Paxil)	10-40 mg/day
Possible Positive Side Effects	
Possible Negative Side Effects	
may be sedating (for patients experiencing sedation with paroxetine, dose at bedtime; can be useful with depression-associated insomnia)	insomnia, agitation (for patients experiencing these effects, administer dose in mornings), nausea, headache, sexual dysfunction in men and women.
When discontinuing paroxetine therapy, carefully titrated dosage reduction is important for avoiding serious adverse effects associated with abrupt discontinuation. Such effects include confusion, agitation, irritability, sensory disturbances, and insomnia.	

Sertraline (Zoloft)	50-100 mg/day
Possible Positive Side Effects	
Possible Negative Side Effects	
may have lower incidence of significant drug-drug interactions compared with fluoxetine and paroxetine; starting with lower dosages is recommended when this medication is used with protease inhibitors	insomnia, agitation, nausea, headache, sexual dysfunction in men and women, long half-life

Citalopram (Celexa) or Escitalopram (Lexapro)	10-60 mg/day 10-20 mg/day
Possible Positive Side Effects	
Possible Negative Side Effects	
may have lower risk of significant drug-drug interactions compared with SSRIs	mild nausea, possible sedation

Venlafaxine XR (Effexor XR)	75-375 mg/day
Possible Positive Side Effects	Possible Negative Side Effects
may have lower risk of significant drug-drug interactions compared with SSRIs.	nausea, headache, nervousness, sexual dysfunction <u>Note:</u> monitor blood pressure at higher dosages of venlafaxine.

Other agents

Other, newer antidepressants such as **mirtazapine (Remeron)** may be particularly useful in patients who have significant insomnia and in patients who have experienced sexual dysfunction caused by other antidepressant agents such as SSRIs. Mirtazapine should be administered at bedtime because of its sedating side effects. Sedation is commonly noted with the 15mg/day starting dosage, but may be lessened by increasing the dosage to 30 mg at bedtime. Individuals also may experience an increase in appetite and weight gain, in addition to dry mouth. Mirtazapine has minimal drug-drug interactions. Therapeutic dosage range is 15-45 mg/day. Consider starting with 15 mg at bedtime for 7 days, then increasing to 30 mg if sedation is problematic.

Bupropion (Wellbutrin) sustained-release (SR) or extended-release (XL) formulation also may be used in individuals with depression who are experiencing sexual dysfunction caused by other antidepressant agents. Bupropion SR or XL dosing should not exceed 400 mg/day (SR formulation should be administered twice daily in divided doses) due to increased risk of seizures at higher bupropion dosages, particularly in individuals who have other risk factors for seizures. For patients taking protease inhibitors, caution should be used as the daily dose approaches 300-400 mg/day due to possible increased levels of bupropion. Bupropion may have an "activating effect," which can be experienced as agitation and/or insomnia in some patients, and also may have an appetite suppressant effect.

Nefazodone (Serzone) may cause liver toxicity and generally is not recommended as an antidepressant within the HIV/AIDS patient population because of high rates of preexisting liver abnormalities in HIV-infected patients. This medication has recently received a black box warning regarding severe liver toxicity from the U.S. Food and Drug Administration. If the patient has ever had liver toxicity from the drug, restarting is contraindicated.

Tricyclic antidepressants may be effective, but in general have a higher risk of side effects and are more dangerous with overdose.

Treatment may involve antidepressant combinations, including psychostimulants.

Patients with prominent insomnia may benefit from the addition of **trazodone** 25-50 mg, given 1-2 hours before bedtime.

Saint-John's-wort is a herbal antidepressant that is contraindicated for use with patients taking HIV medications (protease inhibitors and nonnucleoside reverse transcriptase inhibitors). Saint-John's-wort can significantly decrease serum concentrations of these HIV medications.

Adapted from: AETC Clinical Manual for Management of the HIV-Infected Adult, 2006 Edition, Chapter 7: Neuropsychiatry Disorders. Retrieved from, http://www.aidsetc.com/aetc/aetc?page=cm-702_depression

Interactions between HIV-Related Medications and Psychotropic Medications: Indications and Contraindications

HIV Medication	Contraindicated	Use with Caution	Possible Dose Adjustment
Amprenavir	Alprazolam, diazepam, midazolam, triazolam, zolpidem	<ul style="list-style-type: none"> Fluoxetine and fluvoxamine may increase PI concentration and toxicity. Carbamazepine, Phenobarbital, phenytoin, primidone, St. John's Wort reduce level of PI, and concurrent use should be avoided. Avoid pimoizide if possible. 	Carbamazepine, Phenobarbital, phenytoin levels rise: monitor levels and adjust prn.
Clarithromycin	None identified	St. John's wort may decrease level of clarithromycin	Carbamazepine level rises: monitor level and adjust prn. Initial dose of benzodiazepines (i.e., alprazolam, midazolam) should be reduced, as clarithromycin may increase levels.
Delavirdine	Alprazolam, midazolam, triazolam	<ul style="list-style-type: none"> Fluoxetine, fluvoxamine and nefazodone may increase NNRTI level and increase toxicity. Carbamazepine, phenobarbital, phenytoin, St. John's wort can lower delavirdine levels: avoid concurrent use if possible. Avoid pimoizide if possible. 	Carbamazepine levels may rise: monitor and adjust prn.
Didanosine (ddI)	None identified	Gabapentin levels decreased by antacid: ddI should be given 2 hours before or after.	Methadone decreases ddI: consider increased dose.
Efavirenz	Alprazolam, diazepam, midazolam, pimoizide, triazolam	<ul style="list-style-type: none"> Fluoxetine, fluvoxamine, and nefazodone may increase NNRTI level and increase toxicity. St. John's wort may decrease efavirenz levels and should be avoided. 	<ul style="list-style-type: none"> Methadone levels decreased: may need to increase dose. Carbamazepine levels may rise: monitor and adjust prn.
Fluconazole	None identified	None identified	<ul style="list-style-type: none"> Carbamazepine and phenytoin levels rise: monitor level and decrease dose prn. Due to CNS effects, may need to decrease dose of benzodiazepines (i.e., alprazolam, midazolam, triazolam), methadone, or zolpidem. Levels of amitryptiline and

HIV Medication	Contraindicated	Use with Caution	Possible Dose Adjustment
			nortriptyline may rise: monitor and adjust prn.
Indinavir	Diazepam, midazolam, St. John's wort, triazolam, zolpidem	<ul style="list-style-type: none"> Fluoxetine, fluvoxamine, and nefazodone increase PI level and increase toxicity. Carbamazepine, phenobarbital, phenytoin, and primidone reduce indinavir level. Avoid pimoziide if possible. 	Carbamazepine level rises: monitor and lower dose prn.
Ketoconazole	Alprazolam, clonazepam, diazepam, midazolam, triazolam	None identified	Carbamazepine and ethosuximide levels rise: monitor toxicity and lower dose if necessary.
Lamivudine	None identified	None identified	None identified
Lopinavir/ Ritonavir *	Alprazolam, bupropion, clorazepate, clozapine, diazepam, estazolam, flurazepam, midazolam, pimoziide, St. John's wort, triazolam, zolpidem	<ul style="list-style-type: none"> Fluoxetine, fluvoxamine, and PI levels may increase. Mexiletine levels rise and may cause greater cardiac/neurologic toxicity: use with caution. Phenobarbital and primidone levels may rise and PI level fall: avoid concurrent use if possible. 	<ul style="list-style-type: none"> Desipramine levels may rise significantly: consider 50% lower dose. Meperidine and methadone levels decrease: may need increased dose. Carbamazepine, clonazepam, nefazadone, and sertraline: initial dose should be reduced 70%. Trazodone levels may increase: start low. Phenothiazines, SSRIs, and TCAs should have initial dose reduced by 50% and be monitored closely for toxicity. Valproic acid, phenytoin doses may need to be higher. Ethosuximide level rises: may need to lower dose.
<p>* Dose of ritonavir is lower than when used as a single PI, and the drug-drug impact of ritonavir may be less significant. However, as pharmacologic data are limited, at this time the same cautions and contraindications as with full-dose ritonavir are repeated.</p>			
Nelfinavir	Diazepam, midazolam, St. John's wort, triazolam, zolpidem	<ul style="list-style-type: none"> Fluoxetine and fluvoxamine may increase PI level. Carbamazepine, phenobarbital, phenytoin, primidone may decrease PI: avoid concurrent use if possible. Avoid pimoziide if possible. 	None identified
Nevirapine	St. John's wort	Fluoxetine and fluvoxamine may increase NNRTI level.	<ul style="list-style-type: none"> Methadone levels lowered: may need higher dose. Carbamazepine levels rise, PI level may drop: avoid concurrent use if possible.
Pyrimethamine	Lorazepam increases risk of hepatic toxicity (monitor LFTs).	None identified	None identified

HIV Medication	Contraindicated	Use with Caution	Possible Dose Adjustment
Rifabutin and Rifampin	None identified	None identified	<ul style="list-style-type: none"> • Methadone level decreases, and higher dose may be needed. • Carbamazepine, phenytoin, valproic acid levels may decrease: may need to increase dose based upon levels
Ritonavir	Alprazolam, bupropion, clorazepate, clozapine, diazepam, estazolam, flurazepam, midazolam, pimoziide, St. John's wort, triazolam, zolpidem	<ul style="list-style-type: none"> • Fluoxetine, fluvoxamine, and PI levels may increase. • Mexiletine levels rise and may cause greater cardiac/neurologic toxicity: use with caution. • Phenobarbital and primidone levels may rise and PI level fall: avoid concurrent use if possible. 	<ul style="list-style-type: none"> • Desipramine levels may rise significantly: consider 50% lower dose. • Meperidine and methadone levels decrease: may need increased dose. • Carbamazepine, clonazepam, nefazadone, and sertraline: initial dose should be reduced 70%. • Trazodone levels may increase: start low. • Phenothiazines, SSRIs, and TCAs should have initial dose reduced by 50% and be monitored closely for toxicity. • Valproic acid, phenytoin doses may need to be higher. • Ethosuximide level rises: may need to lower dose.
Saquinavir	Diazepam, midazolam, St. John's wort, triazolam, zolpidem	<ul style="list-style-type: none"> • Fluoxetine and fluvoxamine may increase PI level and toxicity. • Phenobarbital and primidone can lower PI: avoid concurrent use if possible. • Avoid pimoziide if possible. 	Carbamazepine level rises (may need to lower dose prn) and PI falls when co-administered.
Stavudine	None identified	None identified	None identified
Zalcitabine (ddC)	None identified	Disulfuram and phenytoin may increase risk for peripheral neuropathy	None identified
Zidovudine	None identified	Methadone and valproic acid increase zidovudine levels: monitor for toxicity.	None identified

Data are from:

- 1) Klein R, Struble K. *The Protease Inhibitors: Backgrounder*. Food and Drug Administration, September 1996.
- 2) Preston SL, Stein DS. Drug interactions and adverse drug reactions with protease inhibitors. *Primary Psychiatry*. 1997;64:69.
- 3) *Physicians' Desk Reference*. Oradell, NJ: Medical Economics Company, Inc.; 1997.

Adapted from: Appendix I, Table I-1: Interactions between HIV-Related Medications and Psychotropic Medications: Indications and Contraindications. In *Mental Health Care for People with HIV Infection: HIV Clinical Guidelines for the Primary Care Practitioner*. Published March 2001. Developed by the New York State Department of Health AIDS Institute, Mental Health Guidelines Committee. Retrieved 2006 from <http://www.hivguidelines.org/Content.aspx?pageID=261>