

Management of Psychiatric Illness in HIV+ Patients

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Considerations in HIV/Psychiatric Comorbidity

- Psychiatric illness can affect disease course
- HIV illness can affect management of psychiatric illness
- Psychiatric illness is a risk factor in HIV transmission
- HIV infection and HIV meds can cause psychiatric illness
- Substance abuse greatly increases risk for both HIV infection and psychiatric illness

Psychiatric Disorders in HIV Disease

- Depressive Disorders
- Bipolar Disorder
- Psychotic Disorders

Prevalence of Depression

- Prevalence
 - 8-14% in general population (SAMHSA 1996; Wang et al, JGIM 200)
 - Varies greatly by study; up to 33% in HIV+ (Bing et al, Arch Psych 2001)
- Possible reasons for increased prevalence
 - Depression and substance use
 - Depression and sexual risk behavior
 - Depression and chronic/life-threatening illness
 - Subcortical brain damage in late stage disease

Depression Predicts Mortality

Bangsberg, Perry, Charlebois, Karasic, Sorensen, Clark, Dilley, Moss
41st ICAAC 2001, #1721

- Depressive symptoms (BDI>15) is associated with 2.8 (CI 1.2-6.6) times greater risk of death.

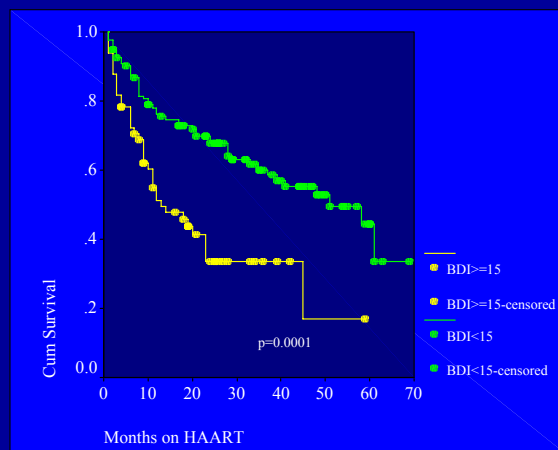
Why Does Depression Speed Progression to AIDS and Death?

- Stress alters cellular and humoral immune response
- Delayed HAART initiation
- Early HAART discontinuation
- Sub-optimal adherence to HAART

Depression and HIV Medication Adherence

- Singh. AIDS, 1996.
- Hozmer. AIDS Patient Care STDs, 1999.
- Peterson. Annals Int Med, 2000.
- Schulz. 38th ICAAC, 1998.
- Bangsberg. 41st ICAAC, 2001: #1721.

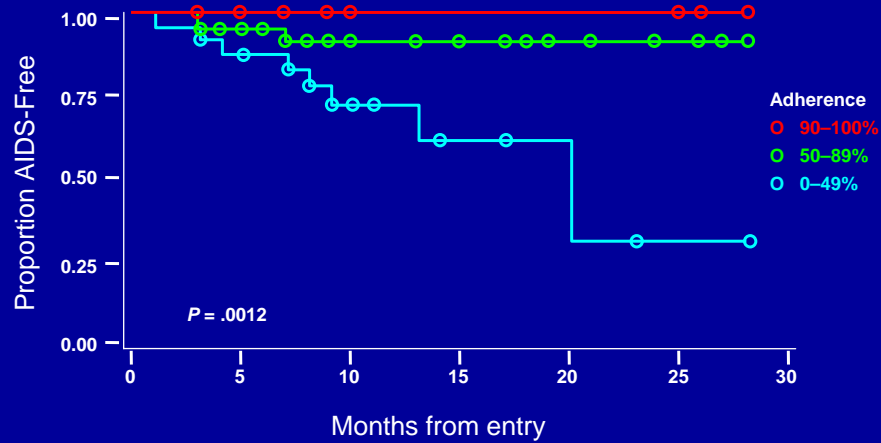
Time to HAART Discontinuation By Depressive Symptoms



Bangsberg, Perry, Charlebois, Karasic, Sorensen, Clark, Dilley, Moss; 41st ICAAC, 2001.

Adherence and AIDS-Free Survival

10% Adherence Difference = 21% Reduction in Risk of AIDS



Bangsberg D, et al. AIDS, 2001;15:1181.

Simple Depression Assessment

1. During the past month, have you often been bothered by feeling down, depressed, or hopeless?

Yes No

1. During the past month, have you often been bothered by having little interest or pleasure in doing things?

Yes No

If “no” to both, patient is unlikely to have major depression.

If “yes” to either, proceed with the follow-up clinical interview.

Whooley MA, Simon GE. *N Engl J Med*, 2000.

Follow-up Interview for Diagnosis

- Depressed mood most of the day almost every day
- Decreased interest and pleasure in usual activities
- Change in appetite or weight
- Disruptions in sleep patterns nearly every day
- Psychomotor retardation or agitation
- Feelings of worthlessness or guilt
- Diminished ability to concentrate
- Recurrent thoughts of death or suicide
- Fatigue/low energy

Depression and adherence studies include bipolar individuals

- Studies that have linked depressive symptoms with increased progression to AIDS and increased mortality measure depressive symptoms; as such include unipolars and bipolars

Bipolar Disorder complicates HIV prevention and treatment

- HIV risk behavior in bipolar pts affects individual and community
- Bipolar disorder affects adherence to HIV medications and health outcomes
- Bipolar depression may not respond to conventional antidepressant therapy

Bipolar Disorder: Prevalence

Bipolar Disorder and secondary mania are more common in HIV+ people

Bipolar Disorder and HIV-Associated Mania

- Bipolar I prevalence 1%, but Bipolar Spectrum Disorders may be 3-5%
- Higher in depressed populations
- Manic syndrome in pts with AIDS may be associated with HIV CNS disease
- Bipolar disorder may increase risk of HIVinfection

Chicken and egg?

- HIV can affect the CNS to cause mania
- Bipolar Disorder may increase risk behavior for HIV

Secondary mania associated with HIV

- Lyketsos (1993) 8% of patients in AIDS clinic had a manic episode in 17 months
- Several studies, pre-HAART, reported cases of secondary mania, often associated with HIV encephalopathy and AIDS dementia
- Organic mania less common with ARVs

Bipolar disorder common in HIV+ patients presenting with depression

| | HIV + | HIV- |
|------------|-------|------|
| Bipolar I | 1 | 4 |
| Bipolar II | 36 | 12 |
| Unipolar | 9 | 30 |

Hyperthymic/Cyclothymic temperaments more common in HIV+

Perreta P, et al. Journal of Affective Disorders 50 (1998) 215-24

Bipolar Disorder common in HIV+ pts in some studies

- In HOME Study, of 1060 participants screened, 28% screened out for bipolar disorder vs 6% enrolled with unipolar depression
- HOME Study population is homeless/marginally housed, with substance abuse common.

Diagnosis of bipolar disorder

- Diagnosis of bipolar spectrum disorders often missed if not specifically asked about: NDMDA: 73% misdiagnosed
- Screening instrument helpful: The Mood Disorder Questionnaire
- Constellation of symptoms happening together, and severe enough to affect functioning makes diagnosis

Diagnosis of Manic Episode

A: 1+ week of elevated or irritable mood

B: 3-4+ of the following at the same time:

grandiosity, decreased need for sleep,
increased speech, racing thoughts/ FOI,
distractibility, increased activity/agitation,
excessive pleasurable/reckless activities

Diagnosis of Manic Episode (2)

C. Not Mixed state

D. Marked social/occupational
impairment, hospitalization, or psychosis

E. Not primarily due to substances or medical
illness

“Bipolar Spectrum”

- Many patients have manic/hypomanic symptoms not meeting full criteria for Bipolar I but still impaired

Psychosis and HIV Disease

- High rates of HIV in schizophrenics:
Needle-sharing and unsafe sex
- Risk of HIV and of psychosis in
methamphetamine and cocaine users
- HIV encephalopathy can cause psychosis
- Psychosis and HIV meds

Treatment

- Depressive Disorders
- Bipolar Disorder
- Psychotic Disorders

Depression Treatments

- Cognitive-behavioral therapy, interpersonal therapy
- Antidepressants
- Alternative medications

Cognitive-Behavioral Treatment of Depression in HIV+ People

| <u>Author</u> | <u>Response</u> | <u>Journal</u> | <u>Year</u> |
|---------------|---------------------|-----------------|-------------|
| Lee | 75% response | Psychiatr Serv | 1999 |
| Mulder | 50%↓ BDI | Psychosom Med | 1994 |
| Kelly | 28%↓ CES-d | Am J Psychiatry | 1993 |
| Targ | Equal to Fluoxetine | Psychosom | 1994 |

Tricyclic Antidepressant Treatment of Depression in HIV+ Individuals

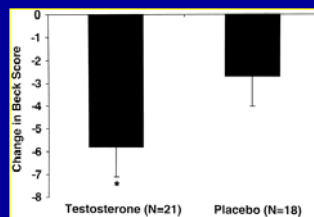
| Medication | Response | Author | Journal | Year |
|-------------|----------|----------|-----------------|------|
| Imipramine | 74% | Rabkin | Am J Psych | 1994 |
| Imipramine | 87% | Elliot | Am J Psych | 1998 |
| Desipramine | 50% | Schwartz | Dep and Anxiety | 1999 |

SSRI Treatment of Depression in HIV+ Individuals

| Drug | Response | Investigator | Journal | Year |
|---------------------------|----------|--------------|-----------------|------|
| Fluoxetine | 83% | Rabkin | J Clin Psych | 1994 |
| Fluoxetine | 64% | Zisook | J Clin Psych | 1998 |
| Fluoxetine | 67% | Elliot | Am J Psych | 1998 |
| Fluoxetine | 90% | Ferrando | Gen Hosp Psych | 1997 |
| Fluoxetine | 75% | Schwartz | Dep and Anxiety | 1999 |
| Fluoxetine/ Sertraline | 78% | Ferrando | J Clin Psych | 1999 |
| Sertraline | 86% | Ferrando | Gen Hosp Psych | 1997 |
| Paroxetine | 86% | Ferrando | Gen Hosp Psych | 1997 |

Treatment of Depression With Other Agents in HIV+ Individuals

| | | | | |
|----------------------------|-----|-----------|----------------------|------|
| Dextroamphetamine | 73% | Wagner | J Clin Psych | 1999 |
| Testosterone | 74% | Rabkin | Arch Gen Psych | 2000 |
| Testosterone (Sx decrease) | | Grinspoon | J Clin Endo Metab | 2000 |



Grinspoon 2000

Sequencing HIV and Antidepressant Treatment: Treat Depression First If Possible

- Depression is common
- Depression is the strongest modifiable predictor of adherence to all medical therapy
- Adherence is the strongest predictor of disease progression and death after CD4 cell count
- Depression should be treated prior to starting antiretroviral therapy
- Patients with severe HIV disease may need concurrent initiation of antidepressant therapy and antiretroviral therapy

Bangsberg JGIM 1999;14:446-8.

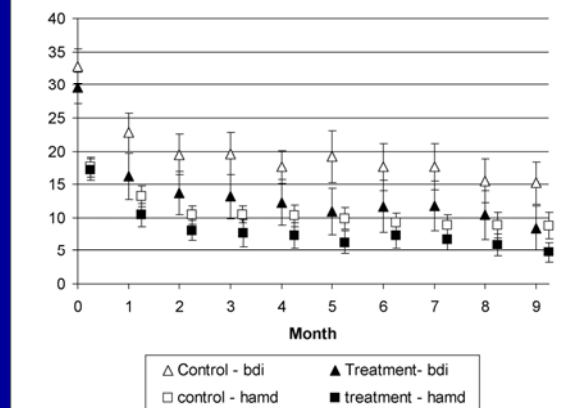
One clinician's treatment strategy for treatment of depression

- SSRI– e.g. fluoxetine/Prozac Weekly, sertraline, or citalopram/escitalopram
- If ineffective, ask about adherence, increase dose to maximum tolerated/recommended
- If still ineffective, augment or substitute with bupropion, mirtazapine, venlafaxine or duloxetine
- 3rd line: Other augmenters, MAOIs (e.g. EMSAM)
- Treat to remission

A case for DOT antidepressants

- UCSF HOME Study: 103 participants diagnosed with Major Depression, Minor Depression, or Dysthymia randomized to receive DOT antidepressants or usual care
- DOT fluoxetine can be dosed weekly
- DOT more effective than usual care in HOME Study
- Consider as treatment strategy in pts who check in weekly

Figure 1: Mean BDI and HAM D Scores and .95 Confidence Intervals by Month for All Participants



Antidepressants and HIV drug interactions

- Antidepressants metabolized by CYP450, primarily 2D6 and 3A4
- PIs and NNRTIs: CYP450 3A4
- Sertraline and citalopram have less effect on P450, but in vivo, all SSRI effect on PI/NNRTI levels not clinically significant
- Venlafaxine may lower PI levels; avoid St. John's Wort
- Ritonavir is strong P450 inhibitor; consider lowering antidepressant dose
 - SSRIs have large therapeutic window; for TCAs check level
 - For bupropion, consider lowering dose; inform pt of possible increased seizure risk

Treatment of Bipolar Depression

- Mood stabilizers lithium and lamotrigine have best antidepressant effect
- Atypical neuroleptics quetiapine and olanzapine/fluoxetine have demonstrated efficacy
- SSRIs and bupropion may have role but...

Treatment of Bipolar Depression

- Preventing mood swings may be key to treating bipolar depression:
 - STEP-BD: Mood stabilizer + antidepressants not better mood stabilizer + placebo in extended study

Treatment of Mania

- Traditional bipolar medications have drawbacks in HIV-positive patients
 - Lithium: increased risk of toxicity, cognitive effects
 - Carbamazepine: P450 inducer lowers PI levels
 - Depakote: Contraindicated with hepatitis

Lithium

- “Gold standard” treatment of bipolar disorder, including maintenance, for past 55 years
- Effective for depression and mania
- May be less effective in secondary mania
- Renal effects, dehydration in AIDS may cause toxicity
- Narrow therapeutic window

Divalproex

- Excellent, fast-acting medication for mania
- Effective in secondary mania and rapid-cycling
- Wide therapeutic window
- Contraindicated with Hep C
- Can cause pancreatitis
- Stimulates HIV replication in vitro (? Clinical significance)

Newer anticonvulsants

- Gabapentin– Not effective as monotherapy; questionable efficacy as augmentation.
- Oxcarbazine
- Lamotrigine- Approved for use in bipolar maintenance.
- Zonisamide

Lamotrigine

- Approved for use in bipolar maintenance
- Effective for bipolar depression
- Requires 6 week titration upward in dosage to avoid risk of severe delayed hypersensitivity reaction
- Effective for HIV neuropathy pain
- No weight gain
- Levels may be decreased by ritonavir

Antipsychotic medications in treatment of bipolar disorder in HIV+ patients

- Older neuroleptics: effective in treatment of mania but poorly tolerated in HIV+ pts
- Atypical neuroleptics effective and well-tolerated in HIV+ pts, but have long term metabolic risks

Treatment Challenges in Psychosis and HIV

- Adherence to HIV meds and to antipsychotics
- Treating psychosis in methamphetamine users
- Sensitivity to dopamine blockers
- Risk of metabolic disorders

Choosing a neuroleptic

Newer medications should be used unless pt is stabilized on older medication and tolerating it well.

HIV-positive patients are at substantially higher risk of EPS and NMS.

Using neuroleptics

- Pt should be warned of small risk of EPS, NMS, and TD.
- Long term use should be periodically reassessed, and metabolic changes, weight changes, and TD symptoms should trigger consideration of alternative medications
- Metabolic risk: varies by drug

Atypical Neuroleptics

- Risperidone: Low incidence of EPS < 6mg in HIV- pts, but pts with symptomatic HIV may get EPS at lower doses.
- Paliperidone: Risperidone metabolite
- Olanzapine: Well tolerated in short term use; best for low weight pts. (D/C Marinol and Megace.) Weight gain and metabolic changes are primary limitation.

Atypical neuroleptics, con't:

- Quetiapine: Very low EPS. Less weight gain than Zyprexa. Sedation and sometimes orthostasis require titration of dose.
- Ziprasidone: Weight neutral. Well-tolerated in longer-term use.
- Aripiprazole: D2 partial agonist. Low weight gain.

Atypical neuroleptics and ARVs

- Metabolic: Adding to ARV risks, atypical neuroleptics can cause weight gain, and increase risk of diabetes and hyperlipidemia
- Drug interactions: ARVs (Protease inhibitors and NNRTIs) and atypical neuroleptics metabolized by CYP450

ARV and atypical neuroleptic drug interactions

- P.I.s and NNRTIs affect CYP450 3A4; ritonavir inhibits multiple isoenzymes
- Quetiapine, aripiprazole, ziprasodone: 3A4 (2/3 of ziprasodone metabolism by aldehyde oxidase, which is not induced/inhibited by ARVs)
- Risperdal: 2D6
- Olanzapine 1A2 (levels decreased by ritonavir)
- Abilify: 3A4

Atypical antipsychotics and HIV drug interactions

- Atypical antipsychotic medications are CYP450 metabolized
- Levels may be affected by PIs, especially ritonavir, but wide therapeutic window provides safety
- Atypicals unlikely to significantly affect PI/NNRTI levels
- (Conventional neuroleptics: lower dose when starting ritonavir.)

Summary

- Psychiatric illness is common in people living with HIV, but often not diagnosed.
- Untreated mental illness decreases HIV medication adherence and increases mortality.
- Detection and proper treatment of mental illness--to remission--may save lives.
- Newer agents have increased safety and tolerability in treating mood and psychotic disorders in persons with HIV/AIDS.