Psychological and Psychiatric Aspects of People Living with HIV

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Emotional/mental health issues throughout the patient journey

- Associated with risk of HIV infection in the first place:
  Risk behaviors: substance abuse, multiple partners
  Mental illness: schizophrenia, bipolar disorder etc.

- Associated with adaptation to HIV status:
  Coping skills
  Strong & stable personality or not
  Realistic perception & Positive appraisal of the future

- Associated with treatment outcome:
  Adherance
  Side effects; lipodystrophy
  Disease progression
Prevalence of mental health issues in people living with HIV

- In a UK survey\(^1\) of 1198 people with HIV:
  - 67% had experienced reported feelings of anxiety or depression in the previous 12 months (not clinically measured or validated measure)

- In a US sample\(^2\) of 2864 adults with HIV:
  - 27.2% were taking psychotropic medication
  - 20.9% were taking antidepressants

Higher prevalence of HIV in people with psychiatric diagnoses

- WHO reported HIV prevalence rates of 5–23% in psychiatric in/outpatients in the USA
  - Compared with 0.3–0.4% in the general US population in 2008
  - 0.2% in the general UK population

<table>
<thead>
<tr>
<th>Country</th>
<th>Number of subjects</th>
<th>HIV prevalence (%) in subjects with psychiatric diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germany</td>
<td>623</td>
<td>4.8</td>
</tr>
<tr>
<td>Italy</td>
<td>475</td>
<td>6.5</td>
</tr>
<tr>
<td>Spain</td>
<td>390</td>
<td>5.1</td>
</tr>
<tr>
<td>USA</td>
<td>Literature review</td>
<td>4–22.9</td>
</tr>
<tr>
<td>USA</td>
<td>11,284</td>
<td>1.2</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>143</td>
<td>23.8</td>
</tr>
</tbody>
</table>

1. WHO HIV/AIDS and Mental Health Report 2008
2. UNAIDS 2008 report (Annexe 1)
Mental health issues may increase risk of HIV transmission

• WHO reported behavioural risk factors for HIV transmission in 30–60% of people with severe mental illnesses¹
  – Sexual contact with multiple partners
  – Sexual abuse
  – Unprotected sex
  – Substance abuse

• Evidence-base?
  – A meta-analysis of 34 study samples concluded that mental/emotional issues (depression, anxiety) are not associated with increased sexual risk behaviour²

1. WHO HIV/AIDS and Mental Health Report 2008
5 stages of emotional adaptation by Kubler-Ross

1. SHOCK & DENIAL  "No, not me!"
   shock, anxiety, fear, panic, depress

2. ANGER  "Why me?"
   anger, fear

3. BARGAINING  "Yes, it is me, but....."
   anxiety, depress

4. DEPRESSION  "Yes, it is me."

5. ACCEPTANCE  anxiety, fear, depress
- DEPRESSION
- ANXIETY DISORDER
- HIV – Associated Neurocognitive Disorders
Depression

- Associated with poor adherence, lowered ART medication and risk behavior
- Most common diagnosis reported

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>n</th>
<th>Diagnosis</th>
<th>Mortality/Progression</th>
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</thead>
<tbody>
<tr>
<td>Ciesla and Roberts, 2001¹</td>
<td></td>
<td></td>
<td>Meta analysis</td>
<td>2-4 x diagnosis depression HIV</td>
</tr>
<tr>
<td>Lima et al, 2007²</td>
<td>Canada</td>
<td>563</td>
<td>51% depression</td>
<td>10% mortality f/up, depression/adherence 5.9 x increased</td>
</tr>
<tr>
<td>Antelman et al, 2007³</td>
<td>Tanzania</td>
<td>996</td>
<td>57% depression</td>
<td>1.6 increased odds of disease progression</td>
</tr>
<tr>
<td>Bing et al, 2001⁴</td>
<td>USA</td>
<td>2864</td>
<td>36% depression</td>
<td></td>
</tr>
<tr>
<td>Pence et al, 2007⁵</td>
<td>USA (Chase)</td>
<td>198</td>
<td>35% depression</td>
<td></td>
</tr>
</tbody>
</table>

3. Antelman et al. JAIDS 2007;44:470–477
5. Pence et al. JAIDS 2007;44:159–166
Depression

- Brief questionnaires for assessment of depression by primary care providers
  - Beck Depression Inventory (BDI)
  - Zung Self-Rating Depression Scale (SDS)
  - The Center for Epidemiologic Studies Depression scale (CES–D)
แนวทางในการประเมินภาวะซึมเศร้า (DSM-IV-TR)

1. มีอารมณ์เศร้า หดหู่ และ/หรือ ไม่สนใจ ไม่มีความสุขกับสิ่งที่เคยชอบ

2. มีอาการดังต่อไปนี้อีก 4 ข้อ
   ก. เบื่ออาหาร, น้ำหนักลด
   ข. นอนไม่หลับหรือนอนมากผิดปกติ
   ค. เลือยซ่าหรือกระวนกระวายนั่งไม่ติด
   ง. อ่อนเพลีย ไม่มีแรง
   จ. รู้สึกตนเองไร้ค่า, รู้สึกผิด, หมดหวัง
   ฉ. ไม่มีสมาธิ คิดไม่ออก ลืมง่าย
   ฉ. คิดถึงความตาย อยากตาย คิดฆ่าตัวตาย
Mental health may affect physical state

- Study cohort of 765 HIV-seropositive women in the US, aged 16–55 years1
  - Chronic depressive symptoms were associated with a significantly greater decline in CD4 cell counts, when other variables i.e. clinical, substance use and sociodemographic characteristics were controlled for1
- 277 HIV-seropositive men in the US2
  - Overall depression and affective depression predicted a more rapid decline in CD4 cell counts2

1. Ickovics. JAMA 2001;285:1466–1474
Adherence reduced in presence of depression

*CES-D, Center for Epidemiologic Studies Depression Scale.

P=0.0242

78% (CES-D≥16* (With depression))

52% (CES-D<16* (Without depression))

Association of depression and adherence with survival

(−): absence of factor; (+): presence of factor; adherence cut-off point was 95%, depressive symptoms cut-off point was 16 points in the CES-D scale.

Lima et al. AIDS 2007;21:1175-1183
Adherence increased with interventions for depression

Subject group: HIV-infected drug users with diagnosed depression

*Also adjusted for: gender (in overall model); age; residence; chronic non-HIV medical condition; acute infection, AIDS; acute illicit drug-related complication; drug dependence; heroin or cocaine abuse/dependence; other drug abuse/dependence; alcohol abuse/dependence.

**Defined as >95%

Suicide

- Thoughts, attempts, completions
- Long history – pre/post ART availability¹
- 31% suicide ideation in a UK HIV population (n=778)²
- 19% in a USA population (n=2909)³
- 38% in a USA rural population (n=201)⁴
- 19% of HIV positive pregnant women population in South Africa self harm (n=242)⁵

ANXIETY DISORDERs

- Generalized Anxiety Disorder
- Panic Disorder
- Phobic Disorder
- Obsessive Compulsive Disorder
- Post-Traumatic Stress Disorder
Anxiety

- Common including generalized and panic attacks
- 16% of the HIV Cost and Services Utilization Study (HCSUS) population diagnosed with generalized anxiety disorder¹
- 29.5% of people living with HIV in Southern US had significant anxiety (CHASE study)²

2. Pence et al. JAIDS 2007;44:159–166
Post-traumatic stress disorder

- 5–42% people have PTSD diagnosis after life threatening disease diagnosis\(^1\)
- 16–54% of HIV +ve experience post traumatic stress\(^2,3,4\) often diagnosed in conjunction with depression\(^5\)
- 27% in conjunction with stigmatizing events (n=190)\(^6\)
- HIV–related and unrelated PTSD impacts functioning, adherence and depression\(^7\)

Prevalence of substance abuse in HIV infected persons in the preceding year

<table>
<thead>
<tr>
<th>substance abuse</th>
<th>HIV+</th>
<th>Community</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol Abuse or Dependence</td>
<td>11%</td>
<td>4%</td>
</tr>
<tr>
<td>Illicit Substance Abuse or Dependence</td>
<td>14%</td>
<td>2%</td>
</tr>
<tr>
<td>Any Substance Abuse Disorder</td>
<td>20%</td>
<td>4%</td>
</tr>
</tbody>
</table>
Treatment Side Effects

- Treatment side effects/adverse events may be directly/indirectly psychological
- Directly psychological (moods, dreams)
- Indirectly psychological as a result of
  - Body changes (lipoatrophy/lipodystrophy/jaundice)
  - Treatment regimen (food, pacing, logistics)
  - Adherence demands (constant reminder)
Psychotropic effects of antiretrovirals

- **Depression:** Abacavir, Efavirenz, Indinavir, Nevirapine
- **Mania:** Didanosine (ddI), Efavirenz, Zidovudine (AZT)
- **Psychosis:** Abacavir, Efavirenz, Nevirapine
- **PTSD:** Efavirenz
- **Vivid dreams:** Abacavir, Efavirenz, Nevirapine
- **Suicidal ideation:** Abacavir, Efavirenz
- **Miscellaneous symptoms:** Efavirenz
Neuropsychiatric side effect of Medications frequently used for HIV pt.

- Co-trimoxazole; depression, apathy, insomnia
- Isoniazid; depression, agitation, hallucination, paranoid
- AmphotericinB; delirium, diplopia, anorexia
- Steroids; depression, mania, psychosis
- Acyclovir; confusion, visual hallucination, insomnia, agitation,
- Vincristine; depression, hallucination, agitation
How to manage psychiatric problems in PLWHA

- Correct Diagnosis: r/o drug-induced

- Counseling is helpful in adjustment, anxiety disorders and mild depression

- Medications:
  - Antidepressant: TCAs, SSRI, SNRI, NSSA
  - Anxiolytics: benzodiazepine
  - Antipsychotics:
  - Atypical neuroleptics: risperidone, olanzepine, quetiapine, aripiprazole, ziprasidone
กระบวนการให้การปรึกษา

Co.  
Greeting  Small Talk  Attending  Opening  Structuring

Cl
Questions  Paraphrase  Reflection  Interpretation  Tracking

Co.
Summary  Focusing  Clarification

Cl
ตั้งใจนำไปปฏิบัติ รู้เป้าหมายและวิธีแก้ปัญหา รู้ปัญหาและวิธีแก้ปัญหา ฟัง Case  Follow-up  Referral  ยุติ Session  Summary

Support  Information  Suggestion  Consequence

สาระสำคัญ ความต้องการ ดำรงใจ สาระสำคัญ ดำรงใจ
Resource activated for successful adaptation to HIV

- **Internal resources:**
  cognitive reappraisal of a situation
  realistic perception of current life events
  Strong self-concept and self-esteem
  Self-control and self-efficacy

- **External resources:**
  Access to medical care
  Family and social support network
  Therapeutic alliance with the care team
  Psychotherapeutic & psychopharmacological support
  Access to social services
  Support with issues regarding confidentiality
Principles to use Psychotropics

- Start with a low dose and titrate to tolerability & response
- Select the simplest dosing regimen possible
- Select an agent with the fewest side effect /interaction.
- Ensure that management is conducted in closed cooperation with the HIV physicians and the rest of the multidisciplinary team.

Anxiety disorders

- Benzodiazepines: precaution of misuse
- SSRIs
- Others antidepressants
- Buspirone

Depression

- **SSRIs** *(Selective Serotonergic Reuptake Inhibitors)*
- **SNRIs** *(Serotonergic & Noradrenergic Reuptake Inhibitors)*
- **NSSA** *(Noradrenergic & Selective Serotonergic Antidepressant)*
- **TCAs** *(Tricyclic antidepressants)*
- **Atypical Neuroleptics:** olanzepine, quetiapine, aripiprazole, ziprasidone
Several Neurotransmitters Are Thought to Be Involved in Regulating Mood

- Norepinephrine (NE)
- Serotonin (5-HT)
- Dopamine

Mood, emotion, cognitive function
- Anxiety
- Irritability
- Motivation
- Energy
- Vigilance
- Drive
- Sex
- Appetite
- Aggression
- Impulsivity
Evolution of antidepressant drugs

- Improved tolerance
- Greater efficacy

TCA

- 5-HT
- NA

SSRI

- 5-HT

SNRI

- 5-HT
- NA
Adverse Effects of Neurotransmitter Activity and Receptor Binding

- Psychomotor activation
- Psychosis
- Sexual dysfunction
- Activating side effects
- Sedation/drowsiness
- Weight gain
- Blurred vision, Dry mouth, Constipation, Sinus tachycardia, Urinary retention, Memory dysfunction
- Priapism
- Postural hypotension, Dizziness, Reflex tachycardia
- Dry mouth, Urinary retention, Erectile dysfunction, Activating effects, Tremor
- Nausea
- GI disturbances
- Sexual dysfunction
- Activating effects
- DA Reuptake inhibition
- DB Block
- 5-HT2 Block
- 5-HT3 Block
- NE Reuptake inhibition
- Alpha1 Block
- Alpha2 Block
- ACh Block
- H1 Block

Adapted from Richelson E. *Current Psychiatric Therapy*. 1993; 232-239.
<table>
<thead>
<tr>
<th>ยา</th>
<th>NaSSA</th>
<th>TCAs</th>
<th>SSRIs</th>
<th>SNRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ยาฆ่า</td>
<td>Remeron SolTab 30 mg (mirtazapine)</td>
<td>Amitriptyline, Nortriptyline Imipramine, Clomipramine, etc</td>
<td>Fluoxetine, Fluvoxamine, Citalopram, Sertraline, Paroxetine</td>
<td>Venlafaxine Duloxetine</td>
</tr>
<tr>
<td>กลไกการออกฤทธิ์</td>
<td>block α2 auto &amp; hetero receptors block ที่ 5-HT2 และ 5-HT3</td>
<td>block reuptake ของ NE และ 5HT และมีฤทธิ์จับกับ α1, adrenoreceptor histamine และ cholinergic receptor</td>
<td>block reuptake ของ 5HT</td>
<td>ขนาดยาสูงๆ (มากกว่า 150 มก.) ออกฤทธิ์ block reuptake ของ NE และ 5HT ขนาดยาต่ำ (75 มก.) ออกฤทธิ์ block reuptake ของ serotonin อย่างเดียว</td>
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<tr>
<td>ขนาดใช้ยา/วัน</td>
<td>15-45 มก./วัน วันละ 1 ครั้ง ตอนเย็นหรือก่อนนอน</td>
<td>75 – 150 มก./วัน</td>
<td>• Fluoxetine, Paroxetine, Citalopram 20 มก./วัน • Fluvoxamine 100 มก./วัน • Sertraline 50 มก./วัน • Escitalopram 10 mg/วัน</td>
<td>75 – 225 มก./วัน</td>
</tr>
<tr>
<td>อาการข้างเคียง</td>
<td>NaSSA</td>
<td>TCAs</td>
<td>SSRIs</td>
<td>SNRI</td>
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<td>----------------</td>
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<td>ปากแห้ง, ตาพร่า, ท้องมึน, ปัสสาวะคลี่, จงชีม, ความดันโลหิตตก, เมื่อเลือดยืด, ห้าใจเต้นไม่เป็นจังหวะ, วิงเวียน, น้ำหนักขึ้น, สบสน, toxic in overdose</td>
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<td>กระสับกระสนยกล้วยเนื้อ กระสับกระสนยอกิจกรรม, กระสับกระสนยอกิจกรรม, กระสับกระสนยอกิจกรรม, กระสับกระสนยอกิจกรรม, กระสับกระสนยอกิจกรรม, กระสับกระสนยอกิจกรรม</td>
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</tr>
<tr>
<td>อาการถอนยา</td>
<td>Remeron SolTab</td>
<td>เกิดปฏิกิริยาระหว่างยาได้เนื่องจาก TCAs มีผลกระทบต่อการทำงานของเอนไซม์ Cytochrome P450</td>
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<td>มีผลกระทบต่อการทำงานของเอนไซม์ Cytochrome P450 (CYP 2D6)</td>
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</tr>
</tbody>
</table>
Selecting an Antidepressant: Potential for Drug–Drug Interactions

Low P450 blockers: Likely to have little impact on metabolism of other drugs

Potent P450 blockers: Potential for strong impact on metabolism of other drugs

Bupropion
Citalopram
Mirtazapine
Venlafaxine

Sertraline

Methylphenidate
Paroxetine
Fluoxetine
Fluvoxamine

## Inhibitory Potential of Antidepressants

<table>
<thead>
<tr>
<th>Drug</th>
<th>3A4</th>
<th>2D6</th>
<th>1A2</th>
<th>2C9/19</th>
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</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td>++</td>
<td>+++</td>
<td>-</td>
<td>++(++)</td>
</tr>
<tr>
<td>Sertraline</td>
<td>(+)</td>
<td>(+++)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>-</td>
<td>+++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>+++</td>
<td>+++</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Citalopram</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Nefaxodone</td>
<td>++++</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>-</td>
<td>(+)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Bupropion</td>
<td>-</td>
<td>++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

- none; + = mild; ++ = moderate; +++ = mild to moderate; ++++ = potent (metabolite) DeVane CL, Nemeroff CB. *Primary Psychiatry*. 2002; 9: 28-57.
Psychosis, Delirium, Bipolar

- Atypical neuroleptics: risperidone (0.5–4 mg), quetiapine (12.5–200 mg)
  low dose in delirium

- BZDs: lorazepam
  low dose in delirium

Drug interactions between antiretrovirals and psychotropics

- Amprenavir (CYP3A4 inhibitor), Ritonavir (may inhibit & induce CYP3A4, inhibits CYP2D6, CYP2C9, CYP2C19):
  - may increase sedation, confusion, respiratory depression effect of Alprazolam, diazepam, midazolam, triazolam
- Lopinavir + Ritonavir (CYP3A4 & CYP2D6 inhibitor)
  - may increase blood levels of citalopram, fluoxetine, bupropion, mirtazapine
Theoretical scheme of ART impact in a body–mind paradigm

Body
- Benefits of ART on physical wellbeing
  - Immune reconstitution
  - Viral suppression (in plasma)
  - Resolution of HIV symptoms
- Visible side effects
  - Lipatrophy
  - Lipodystrophy
  - Jaundico (yellow skin and eye)
  - Other body-physical changes (BPC)

Mind
- Benefits of ART on mental / emotional wellbeing
  - CNS protection
  - Viral suppression in CSF
  - CNS Penetration-Effectiveness (CPE)
- CNS and psychosocial side effects
  - CNS adverse events
  - Depression, mood and emotional disturbance
  - Psychosocial burden

Impact of ART
+ve

Adherence and behaviour

Treatment outcomes

Quality of life

Switching

Satisfaction
Body physical changes are among the most stigmatising adverse events for patients

- Body physical changes
  - Lipoatrophy
  - Lipohypertrophy
  - Skin colour changes
  - Yellow eye

- Psychological effects
  - Low self-esteem
  - Decreased self-confidence
  - Anxiety and depression
  - (Fear of) disclosure

- Social effects
  - Impaired quality of social relationships
  - Social alienation

- Physical effects

- Sexual dysfunction

- Decreased quality of life

- Decreased adherence
Quality of relationships is affected by perception of visible lipoatrophy

- Probability of having a good or excellent relationship with friends and family was lower (odds ratio, 0.38–0.39) in HIV-positive outpatients (N=457) with self-perceived peripheral fat loss (P=0.001)\(^1\)

- In a survey of 33 HIV-positive patients, body-fat changes were associated with the following \(^2\)
  - Social withdrawal
  - Forced disclosure of HIV status due to facial lipoatrophy
  - Poor body image
  - Low self-esteem

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Increased switching is associated with psychological and physical burden.

Switching ARTs for any reason = decreased QoL

EQ-5D QoL measures:
- Anxiety/Depression
- Pain & discomfort
- Usual activities
- Self Care
- Mobility

Factors that may impact cognitive functioning

- AIDS Dementia
  - Occurrence, end stage disease, effects of treatment, manifestation
- Memory
- HIV action in the brain and central nervous system
- Predisposing personality
- Premorbid psychological/psychiatric factors
- Neuropsychiatric effects of HIV medications
- Psychological impact of HIV diagnosis and treatment
HIV and CNS involvement

- Retrovirus (HIV 1 & 2 – west africa)
- Bind to receptors of CD4 (T lymphocyte), blood monocytes, macrophages, dendrite cell, chemokine co-receptors (CCR5, CXCR4)
- CNS infection: encephalitis with reactive astrocytosis, multinucleated giant cell, activated macroglia, infiltration of monocytid cells, myelin pallor, vacuolar myelopathy
- Seen in central white matter, frontal cortices, basal ganglia, thalamus & brain stem
Epidemiology of cognitive impairment

- Before the introduction of HAART, up to 50% of PLWHA developed HIV-associated dementia at the late stage of HIV/AIDS¹
- Today, neurological impairment affects approximately 60% of HIV-infected patients²

Changing epidemiology declining incidence of HIV dementia

HIV Dementia incidence rate (per 1000 person-years)

HAART introduced

Calendar year

Changing epidemiology rising prevalence of HIV dementia

Due to improved survival rates, the cumulative prevalence of HIV dementia has risen

HIV-associated neurocognitive disorders and CNS side effects of ART

- HIV-Associated Neurocognitive Disorders (HAND) affect up to 50% of PLWHA\(^1\)
- HAND criteria covers 3 possible diagnoses based on severity:\(^2\)
  - asymptomatic neurocognitive impairment (ANI)
  - HIV associated mild neurocognitive disorder (MND); and
  - HIV associated dementia (HAD)
- HAND diagnosis is determined by assessing areas of neurocognitive functioning known to be affected by HIV infection (e.g., executive functions, memory, speed of information processing, motor skills, language)
- BHIVA guidelines: important to select an ART that will not exacerbate mental health side-effects\(^3\)
  - E.g. mania, depression, schizophrenia, bipolar disorders and substance use and risk of addiction\(^4\)

Definition of HIV Associated Neurocognitive Disorder (HAND)

<table>
<thead>
<tr>
<th></th>
<th>No Pre-existing Cause</th>
<th>Delirium Absent</th>
<th>Acquired Impairment in ≥ 2 Cognitive Abilities</th>
<th>Interferes with Daily Functioning</th>
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<tr>
<td>Asymptomatic Neurocognitive Impairment (ANI)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Mild Neurocognitive Disorder (MND)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Mild</td>
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<tr>
<td>HIV-Associated Dementia (HAD)</td>
<td>Yes</td>
<td>Yes</td>
<td>Marked</td>
<td>Marked</td>
</tr>
</tbody>
</table>

Previous names: HAD, ADC

Clinical features of HAND: functional impairment

- Activities of daily living
  - Medication adherence\(^1\)
  - Driving (2-3 times as likely to fail tests)\(^2\)
  - Household finances
  - Meal preparation

- Vocational functioning
  - 5 times more likely to complain of problems performing their jobs
  - Twice as likely to be unemployed

Clinical features of HAND: earlier mortality

The elevation in mortality risk for subjects with minor cognitive motor disorder was statistically significant (RR, 2.2; 95% CI, 1.2-3.8; P < .01)