Clinical Diagnosis: When should Neurocognitive Impairment be Suspected?

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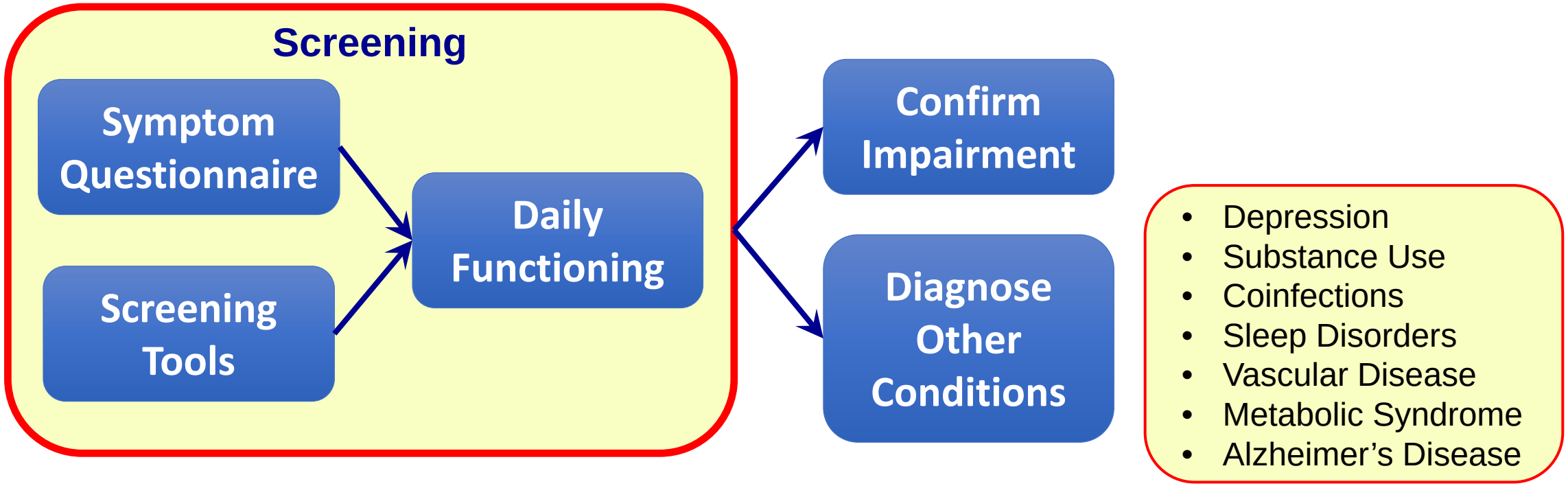
Overall Approach to Screening and Diagnosis



Which patients should be screened for HAND, and when? How often should patients be screened?

- **Assess all patients with HIV** (CEBM 5)
  - Can assist in treatment and management decisions, provide reassurance, and detect cognitive, behavioral and mood changes before symptoms arise or are acknowledged (CEBM 2b)
  - There is no rationale for screening only symptomatic patients (CEBM 2b)
- **Screen patients early in disease using a sensitive tool** (CEBM 5)
  - Screen within 6 months of diagnosis (CEBM 5)
- **Screen patients before ART initiation, if possible** (CEBM 5)
- **Screen every 6–12 months in higher-risk patients or every 12–24 months in lower-risk patients** (CEBM 5)

Clinical Infectious Diseases 2013; 56(7):1004-17

Controversies in HIV-associated neurocognitive disorders

Sam Nightingale, Alan Winston, Scott Letendre, Benedict D Michael, Justin C McArthur, Saye Khoo, Tom Solomon

Lancet Neurol 2014; 13: 1139–51

People with HIV should be screened for ANI

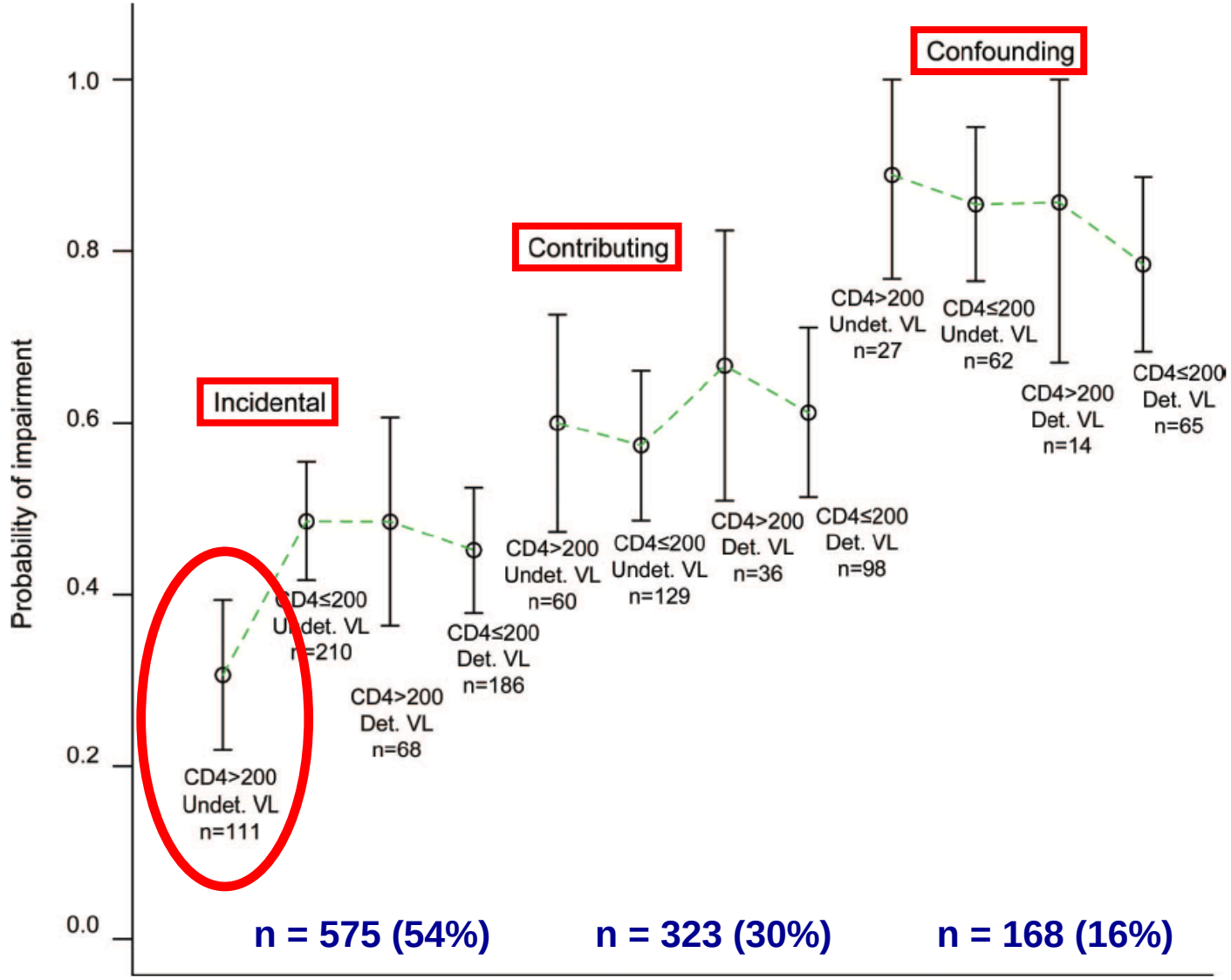
In Favor

- ANI is typically more common than MND or HAD; therefore, cognitive impairment would go unrecognized without screening
- ANI is associated with poor quality of life, poor adherence to medication, and unemployment
- ANI might be associated with an increased risk of progressive neurocognitive disease
- A negative test result on screening might reassure HIV seropositive patients who are aware of the high prevalence of ANI

Against

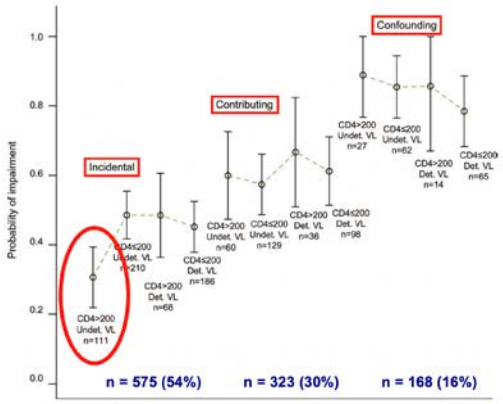
- There are no screening tools for ANI with high sensitivity and specificity that can be used in all clinical settings
- There is no consensus on the therapeutic management of ANI
- Patient screening could lead to diagnostic procedures that might be unnecessary, costly, and invasive
- Worse outcomes in patients with ANI might be related to comorbidities
- A positive result on screening might cause psychological distress to some patients
- Screening for ANI uses clinical resources which are limited

Conditions Other than HIV Strongly Influence the Risk of Neurocognitive Impairment



Heaton, et al. Neurology, 2010, 75:2087–2096

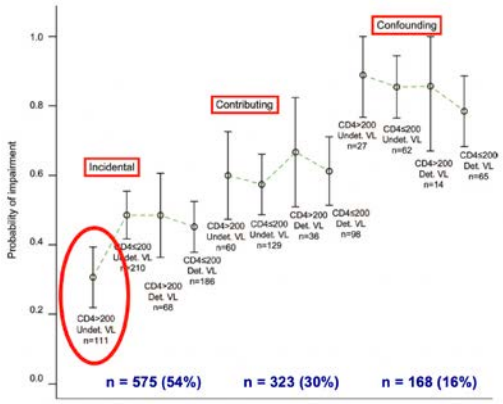
Comorbidity Group Comparisons



	Minimal 575 (54%)	Moderate 323 (31%)	Severe 168 (15%)
Low Reading Level (<80)	15%	28%	49%
Special Education	3%	15%	32%
Other School Problems	5%	40%	52%
Brain Trauma	3%	30%	41%
Cerebrovascular Events	0%	8%	18%
Seizure History	2%	13%	28%
Systemic Medical Condition	27%	56%	64%
Complicated Substance OD	2%	13%	15%
Psychotic Disorder	3%	17%	17%

Slide Courtesy R. Heaton

Comorbidity Group Comparisons



	Minimal 575 (54%)	Moderate 323 (31%)	Severe 168 (15%)
Neurocognitively Impaired (%)	41%	59%	84%
Employed (%)	33%	20%	13%
Depression (Beck Depression Inventory)	12.3 (10.0)	15.7 (11.1)	16.5 (11.9)
Cognitive Symptoms (PAOFI)	4.9 (6.3)	7.4 (8.0)	9.3 (9.0)
Instrumental Activities of Daily Living Declines	1.3 (1.8)	1.9 (2.1)	2.1 (2.3)

PAOFI = Patient's Assessment of Own Functioning Inventory

Slide Courtesy R. Heaton

Focus on Higher Risk Patients

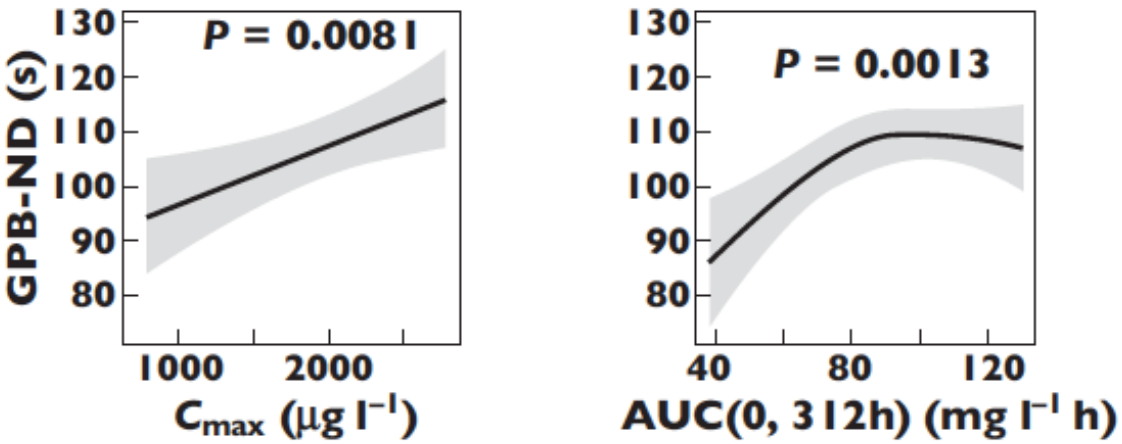
Evidence-supported risk factors	Risk Factor/Comorbidity for HAND and/or Non-HIV-Related NCI	Can Assist Identification of Patients: With Current HAND	At Risk of Developing HAND in Future	At Risk of Non-HIV-Related NCI	CEBM Levels (See Question Details for References)
Readily assessable in clinic					
Disease factors	Low nadir CD4+ T-cell count	X	X		CEBM 1b
	High plasma HIV RNA; high CSF HIV RNA	X	X		CEBM 2b
	Low current CD4 (pre-cART)	X	X		CEBM 2b
	Presence of past HIV-related CNS diseases	X	X		CEBM 1b
	Longer HIV duration	X	X		CEBM 2b
Treatment factors	Low cART adherence	X	X		CEBM 1b
	Episodes of cART interruption	X	X		CEBM 2a
	Nonoptimal cART regimen	X	X		CEBM 2a
	Short cART duration (related to treatment failure)	X	X		CEBM 1b
Comorbidities	Positive HCV serostatus with high HCV RNA	X	X	X	CEBM 1b
	History of acute CV event			X	CEBM 1b
	CV risk factors (hyperlipidemia, elevated blood pressure, chronic diabetes, and diabetes type II)			X	CEBM 1/2b
	Anemia and thrombocytopenia	X	X	X	CEBM 1/2b
Demographic factors	Older age	X	X	X	CEBM 1b
	Low level of educational achievement	X	X	X	CEBM 2b
	Ethnicity	X	X	X	CEBM 2b
	Sex (female, as associated with lower socioeconomic status in some countries)	X	X	X	CEBM 3a
	Lack of access to standard care; poverty	X	X	X	CEBM 3b
Other neurological and psychiatric factors	Neuropsychiatric disorders, eg, MDD, anxiety, PTSD, psychosis, bipolar disorder (current or history of)	X	X	X	CEBM 2b
	Illicit drug/alcohol abuse/dependence (current or history of)	X	X	X	CEBM 2a
	Syphilis or systemic infection	X	X	X	CEBM 2b
	Alzheimer's disease			X	Use APA (in press)
	Cerebrovascular disease			X	Use APA (in press)
	Traumatic brain injury and seizure	X	X	X	CEBM 2b
	Vitamin or hormone deficiency			X	Use APA (in press)
	Prior HCV coinfection*			X	CEBM 2b
Complex cART factors	Lower CPE	X	X		CEBM 2a
	cART neurotoxicity			X	CEBM 3b
Difficult to assess in clinic					
Biomarkers	Abnormal CSF neopterin	X			CEBM 2a
	Abnormal plasma HIV DNA	X			CEBM 2b
	Abnormal NFL	X			CEBM 2a
	Abnormal MCP-1	X			CEBM 2a
	Abnormal serum osteopontin	X			CEBM 4

- **Lower nadir or current CD4+ T-cells**
- **Higher HIV RNA**
- **Poor adherence**
- **Anemia**
- **Older age**
- **Vascular disease risk factors**
- **Substance use**
- **Coinfections**

Mind Exchange Program, Clinical Infectious Diseases 2013; 56(7):1004-17

Antiretroviral Neurotoxicity

Efavirenz

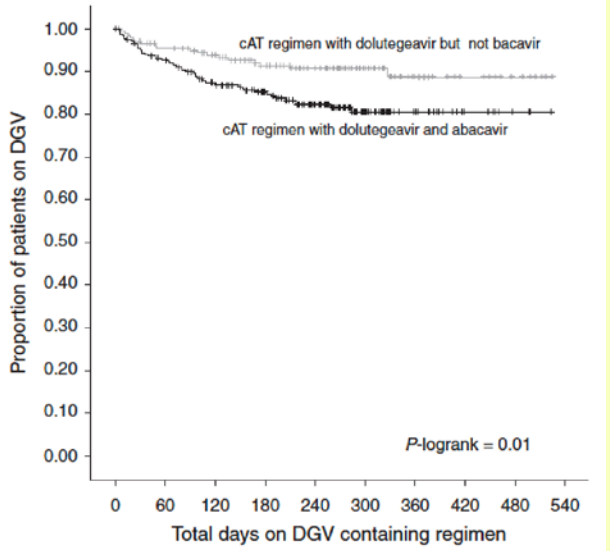


Johnson et al, Br J Clin Pharmacol 2012, 75: 997–1006

Risk Factor	Odds Ratio	P Value
Age (per 10 years)	0.83	0.29
Education (per 1 year)	0.85	0.002
Non-Italian Born	3.5	0.056
Efavirenz use	**4.0**	**0.008**

Ciccarelli et al, Neurology 2011, 76: 1403

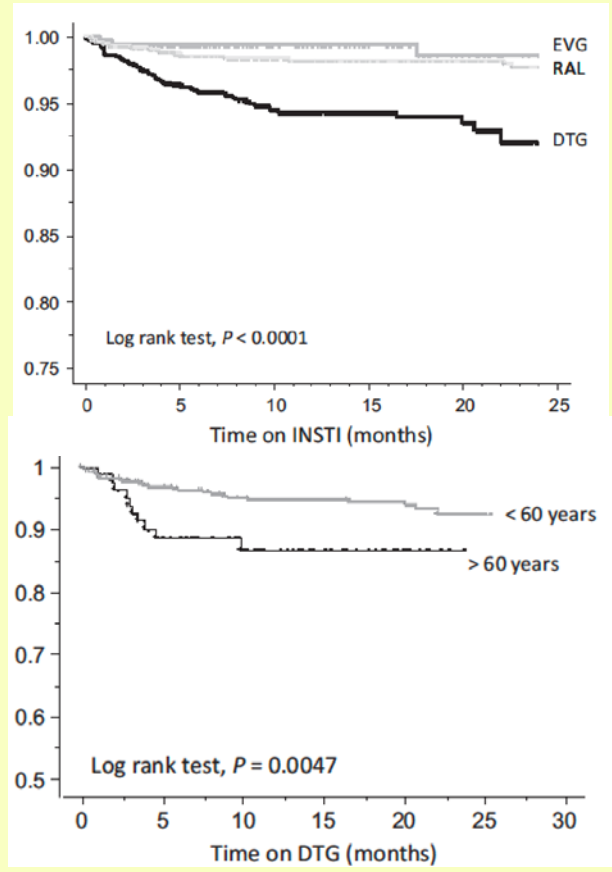
N=565 DTG Only



Adverse drug reaction	*n* (%)
Sleep disturbance, insomnia	31 (5.6)
Gastrointestinal complaints	21 (3.8)
Joint, tendon and/or muscle pain	11 (2.0)
Psychological/psychiatric symptoms[b]	14 (2.5)
Neurologic symptoms	10 (1.8)
General malaise (headache and severe fatigue)	24 (4.3)
Respiratory tract complaints	5 (0.9)
Other	9 (1.6)

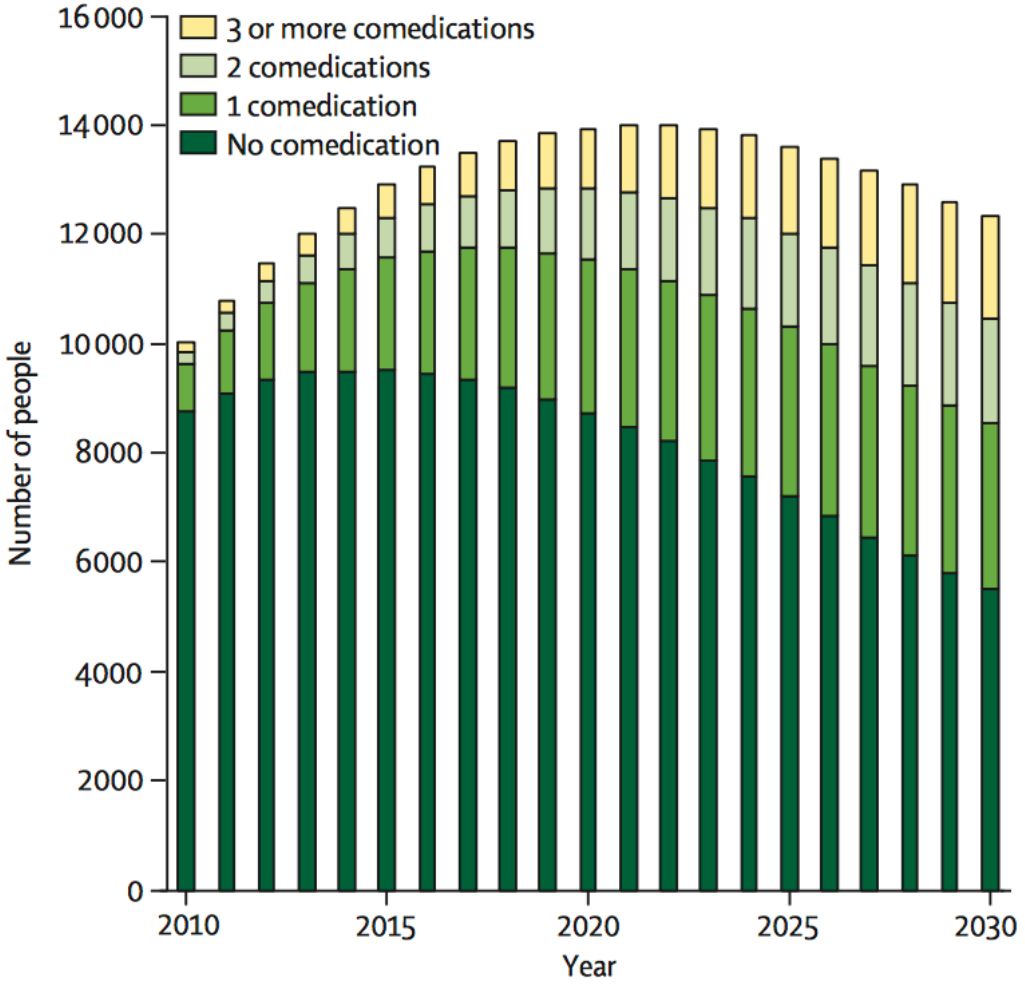
de Boer et al, AIDS 2016, 30:2831–2834

N=1,950 InSTIs Only

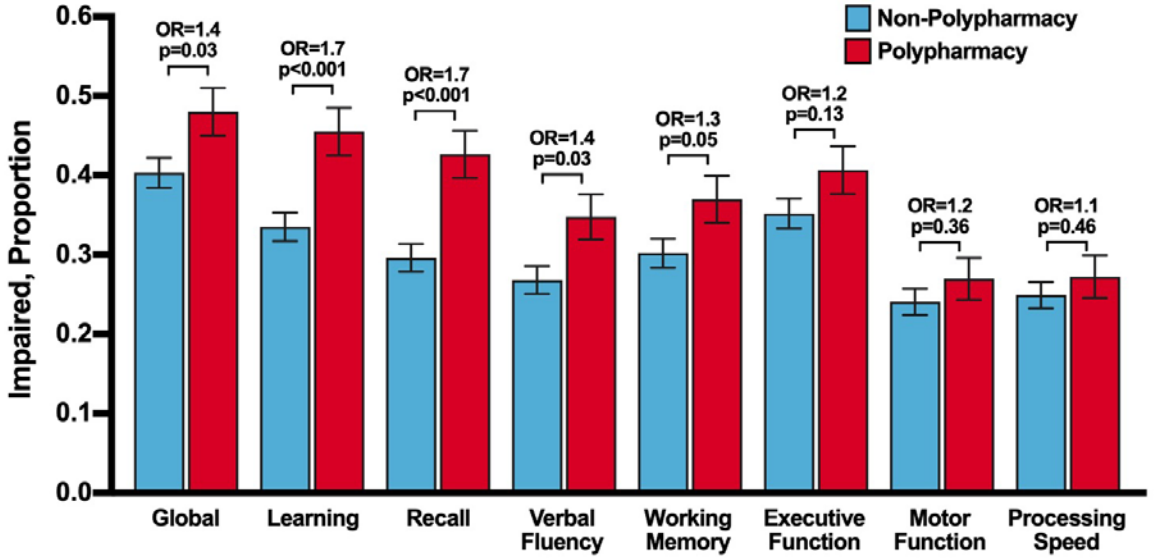


Hoffmann et al, HIV Medicine 2017, 18, 56--63

Risks of Polypharmacy in Aging PLWH



Smit, et al Lancet Inf Dis 2015, 15(7):810-8



	Learning	Executive Function	Working Memory	Recall	Processing Speed	Motor Function	Verbal Fluency
Anxiolytics	**	**	**	**	**	-	*
Antipsychotics	**	**	**	**	-	*	**
Opioids	**	**	**	*	**	*	-
Antimicrobials	**	**	-	**	*	-	-

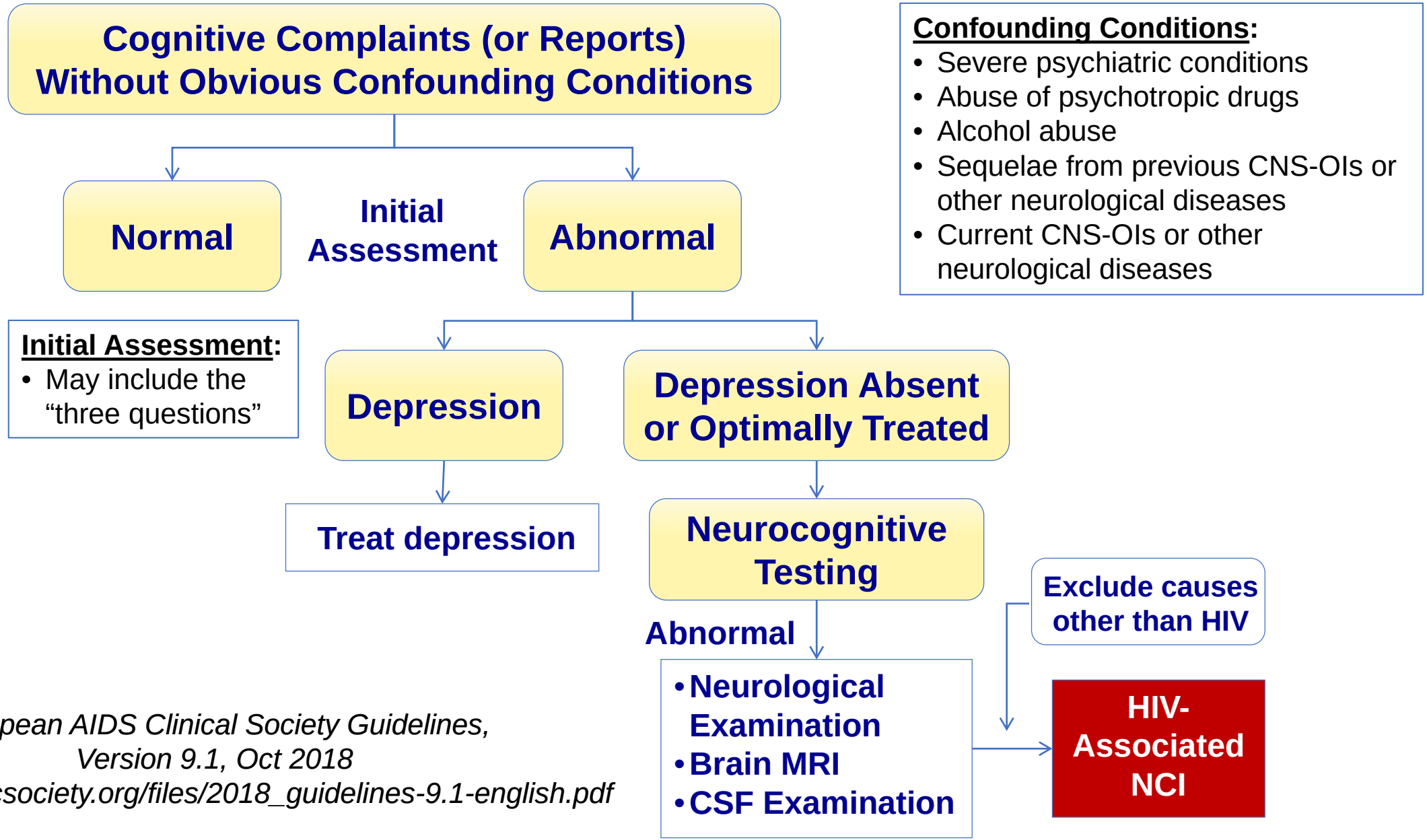
** (Red): p < 0.01, * (Yellow): p < 0.05, - (Green): p > 0.10, statistical significance

Ma, et al CROI 2019, Abstract 437

Genes/processes dysregulated in HAND	Clinical phenotype(s) evaluated[1]	Study design(s)	Replication status[2]
Nuclear genes			
Neuro-degenerative			
APOE (E4 allele)	AIDS with ADC/HAD±HIVE; non-AIDS with HAND±neuropathologic features	Autopsy (mostly case-control; one survival study with autopsy component; 2 uncontrolled); cross-sectional; longitudinal cohort	R
Immune			
TNFA	HAD; HAD/ADC, or HIVE and/or HIV-LE	Autopsy case-control	NR
MCP1/CCL2, CCR2	HAD±HIVE or AIDS/ADC, *OR* change in executive functioning and processing speed between 2 consecutive visits up to 15 yrs apart; or NCI (clinical rating score≥5); HAE (children)	Retrospective case-control; longitudinal cohort±cross-sectional analysis	R (*MCP1*) NA (*CCR2*)
MIP1A/CCL3	HAD; AIDS with HAD; *OR* change in executive functioning and processing speed between 2 consecutive visits up to 15 yrs apart; *OR* risk of NCI	Retrospective case-control; longitudinal cohort	R
SDF1	Decline in NC test scores and/or brain growth failure in children; *OR* change in executive functioning and processing speed between 2 consecutive visits up to 15 yrs apart; *OR* prevalent NCI (adults); change in GDS or cross-sectional GDS in co-HCV+	Longitudinal cohort with cross-sectional component; retrospective case-control	NR
MBL2	Changes in GDS or cross-sectional GDS in co-HCV+; *OR* change in executive functioning and processing speed between 2 consecutive visits up to 15 yrs apart; *OR* prevalent NCI (adults)	Longitudinal cohort with cross-sectional component	NR
CCR5 (δ32 del)	HAD/ADC; AIDS±HAD; decline in NC test scores and/or brain growth failure in children; NCI in children; GDS (change and cross-sectional)	Longitudinal cohort±cross-sectional component; case-control	R prior to 1991 only; NR in cART era
Dopamine			
COMT	Executive functioning domain Deficit Scores±stimulant abuse; HAND: standardized NP domain T-scores	Retrospective/Case-control	NR
DRD2, DRD3	GDS≥0.5 (NCI); Global and cognitive domain T-scores in population with prevalent substance dependence	Cross-sectional/Case-control	R (DRD3 in substance users)
HLA:DR, DQB1, A24, B27	Time to CNS impairment ("deterioration in brain growth, psychological function and/or neurological status")	Pre-cART cross-sectional study; cART era case-cohort study; longitudinal cohort	R (*DR, B27*) NA (*DQB*) NR (*HLA A*)
APOBEC3G	Brain growth failure, with NCI defined differently based on age	Pre-cART pediatric cohort study	NA
PKNOX1/PREP1	AIDS with dementia	Retrospective case-control	NA
YWHAE	HAND	Cross-sectional study with HIV+/HIV- controls	NA
Mitochondrial & Epigenetic			
Mitochondrial & nuclear DNA structural changes			
8-oxoG modification	HAND "screen", International HIV Dementia Score≤10	Autopsy case-control	NA
Regulation of telomere length	Detailed NP test scores (global and ability domain scores)±history of chronic psychological trauma (Childhood Trauma Questionnaire Short Form)	Cross-sectional with HIV+/HIV- controls	NA

Kallianpur & Levine, Curr HIV/AIDS Rep (2014) 11:336–352

EACS Guidelines 2018



European AIDS Clinical Society Guidelines, Version 9.1, Oct 2018
http://www.eacsociety.org/files/2018_guidelines-9.1-english.pdf

Recent Review of NeuroHIV Risk Factors

Table 1 Risk factors (and the degree of association) for HIV-associated neurocognitive disorders and published beneficial interventions

Variable	Degree of association with HAND	Degree of association with ARVs' choice	Other relevant factors	Beneficial interventions
Low CD4 nadir	High	–	–	None
High HIV DNA	Moderate	Low	Duration of viral suppression	None
Plasma HIV RNA	High	High	Several	Genotype-based, adherence
CSF HIV RNA	Moderate	High	Several	Unclear
Symptomatic CSF escape	High (neurological symptoms)	High	Low nadir CD4, resistant-associated mutations	Genotype-based, CNS-targeted
Asymptomatic CSF escape	Low	Moderate	Plasma HIV RNA	Unclear
Residual CSF HIV RNA	Unclear	Unclear	Duration of viral suppression	None
Macrophage-derived cell infection	Low	Moderate	Viral tropism	None
Compartmental immune activation/inflammation	Moderate	Unclear	Low nadir CD4	None
Neurotoxicity	Moderate	High	Host genetics	Unclear
Cardiovascular risk profile	High	Moderate	Several	None

Calcagno et al, Current HIV/AIDS Reports (2018) 15:84–91

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