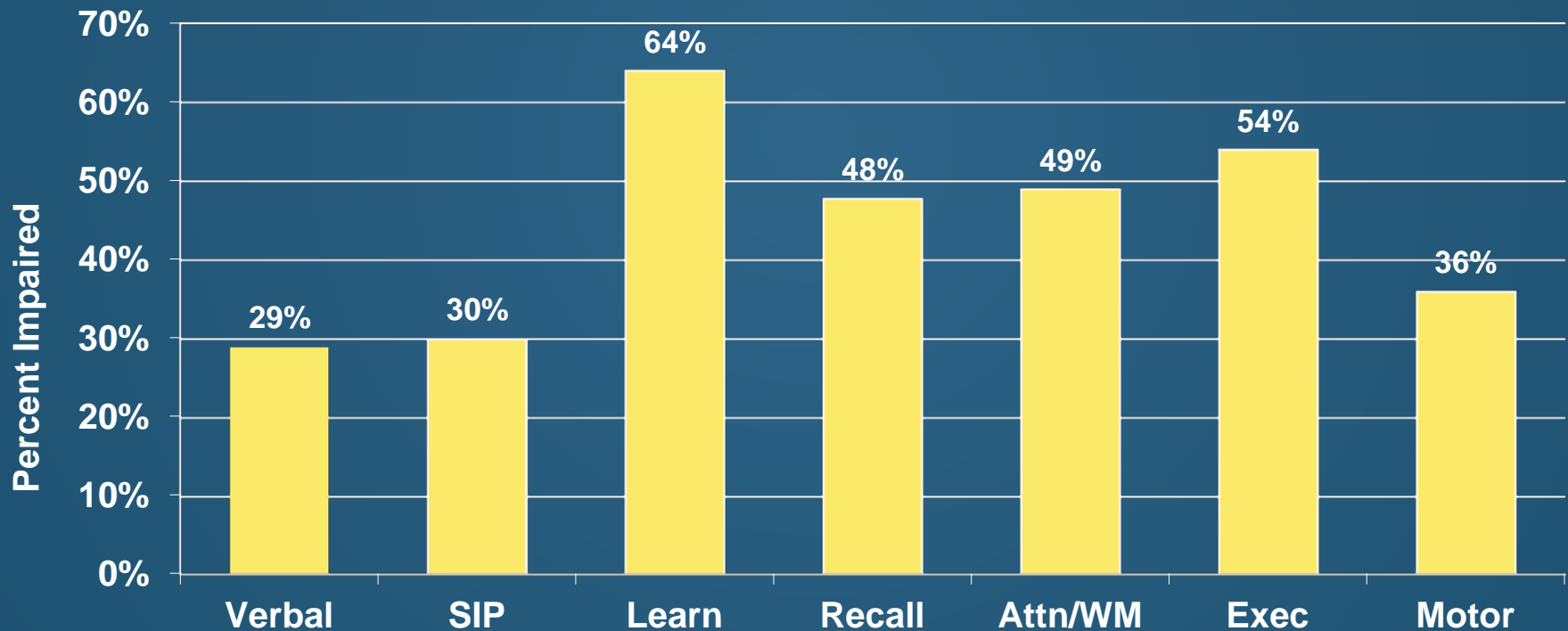


# Assessing HIV Associated Neurocognitive Disorders (HAND) with the NIH Toolbox Cognition and Emotion Batteries

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- HIV Associated Neurocognitive Disorders (HAND) remain highly prevalent (~35-50%) in the cART era, even with suppressive therapy
- Typically mild to moderate in severity and non-progressive, although some cognitive fluctuations can occur (e.g., with changes in treatment)



# HIV Associated Neurocognitive Disorders (HAND) Criteria

	ASYMPTOMATIC NEUROPSYCHOLOGICAL IMPAIRMENT (ANI)	MILD NEUROCOGNITIVE DISORDER (MND)	HIV-ASSOCIATED DEMENTIA (HAD)
NEUROCOGNITIVE IMPAIRMENT	≥ Mild	≥ Mild	≥ Moderate
FUNCTIONAL IMPAIRMENT	None	≥ Mild	≥ Moderate

Impairment must be attributed to HIV, at least in part.  
 “Minimal” or “Moderate” comorbidities are OK, but  
 “Severe” conditions preclude diagnosis of HAND  
 in baseline evaluations.

# Frascati Definition of Neuropsychological Impairment

- At least mild impairment in at least 2 ability domains
- **Mild**:  $> 1$  SD below mean on **demographically corrected** scores in  $\geq 2$  ability domains
- **Moderate-Severe**:  $> 2$  SD below mean on  $\geq 2$  ability domains, or  $> 2.5$  SD below mean on one domain and at least  $> 1$  SD on another domain

# Frascati Comorbid Conditions

- **MINIMAL**: could have minor effects on NP test results, but unlikely to cause even mild global impairment (does not preclude diagnoses of HAND).
- **MODERATE**: likely to have at least mild effects on NP test results but cannot fully explain the nature and/or timing of observed impairment or disability (does not preclude diagnoses of HAND).
- **SEVERE**: likely to have major effects on NP test results, with significant neurocognitive impairment and functional disability, or NP results invalid due to poor effort (precludes diagnoses of HAND at baseline assessment).

# Comorbidity Group Comparisons: Common Non-HIV Factors in US HIV+ Adults

	Minimal 843 (54%)	Moderate 473 (31%)	Severe 239 (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%

# “Gold Standard” Neurocognitive Test Battery (2+ Hours)

- **Verbal Fluency**
  - » Letter Fluency
  - » Category Fluency
- **Speed of Information Proc.**
  - » Wechsler Symbol Search
  - » Wechsler Digit Symbol
  - » Trail Making Test Part A
- **Attention/Working Memory**
  - » Paced Auditory Serial Addition Test - 50
  - » Wechsler Letter-Number Sequencing
- **Motor (DH, NDH)**
  - » Grooved Pegboard
- **Abstraction/Executive**
  - » Wisconsin Card Sorting Test 64
  - » Trail Making Test Part B
- **Learning and Memory**
  - » Hopkins Verbal Learning Test-R
  - » Brief Visuospatial Memory Test-R

# Multisite US HIV Study (N=1555)

## Comorbidity Group Comparisons

	Minimal 843 (54%)	Moderate 473 (31%)	Severe 239 (15%)	
% NC Impaired	41%	59%	84%	Min<Mod<Sev
% Employed	33.0%	19.7%	13.0%	Min>Mod,Sev
Depression (BDI)	12.3 (10.0)	15.7 (11.1)	16.5 (11.9)	Min<Mod, Sev
Cognitive Symptoms (PAOFI)	4.9 (6.3)	7.4 (8.0)	9.3 (9.0)	Min<Mod<Sev
IADL Declines	1.3 (1.8)	1.9 (2.1)	2.1 (2.3)	Min<Mod, Sev



# Association of Neurocognitive Impairment with Everyday Functioning (Severe Comorbidity excluded)

	p-value
Unemployment	.005
IADL Dependence	.0002
Cognitive Symptoms	<.0001

# NIH Toolbox Cognition Battery

## ❖ 30 minute computerized battery

1. Executive Functions
  - Flanker Inhibitory Control and Attention Test
  - Dimensional Change Card Sort Test-Set Shifting
2. Episodic Memory
  - Picture Sequence Memory Test
3. Processing Speed
  - Pattern Comparison Test
4. Working Memory
  - List Sorting Test
5. Language
  - Picture Vocabulary Test
  - Oral Reading Recognition Test



# Fluid vs. Crystallized Abilities

## ❖ Fluid

- Peaks in early adulthood, decreases with older age
- Dynamic thinking
  - e.g., problem solving, learn/recall, speed
- Sensitive to brain injury

## ❖ Crystallized

- Rapid development in childhood, stabilizes (improves) with age (experience)
- Learned life/school experiences
  - e.g., reading, vocab
- Not sensitive to brain injury (stable/“hold” abilities)

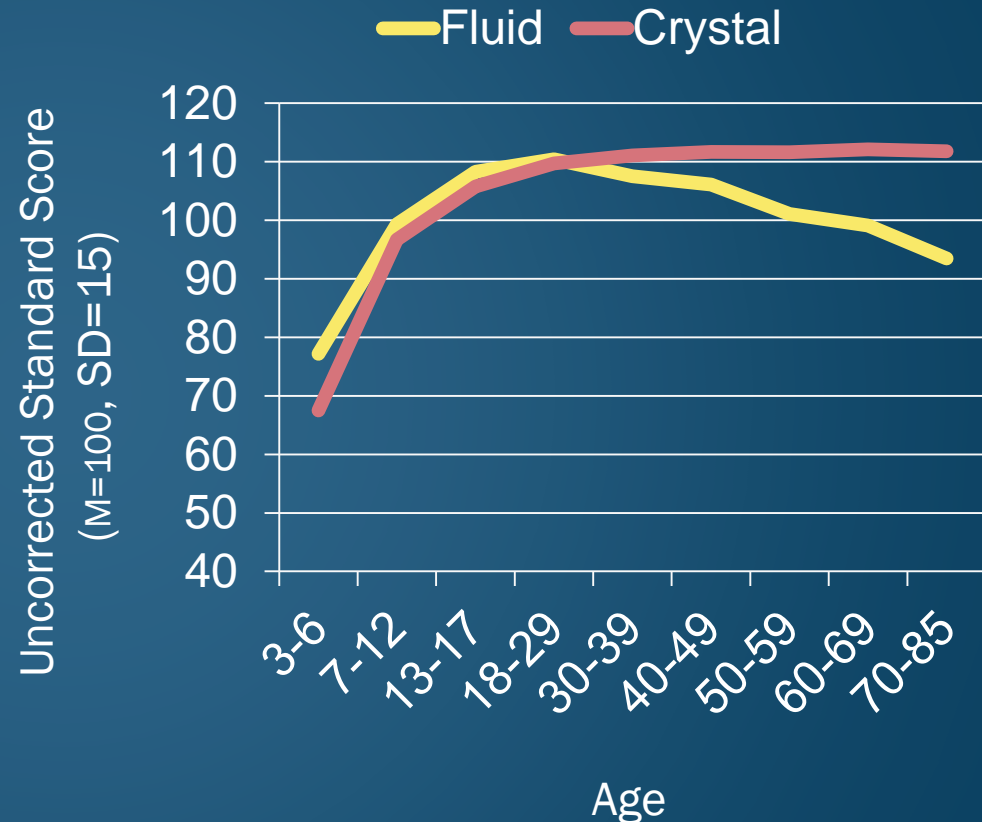


Figure: Casaletto et al. (2015) *JINS*.

# 298 Demographically Matches Pairs of HIV+ and HIV- Adults with Complete Results on NIHTB-Cognition Battery

	<u>HIV+</u>	<u>HIV-</u>
Age	51.0 (11.7)	51.0 (11.9)
Education	14.0 (2.4)	14.0 (2.5)
% White/Asian	67.5	67.5
% Black	17.1	17.1
% Hispanic	15.4	15.4
Gender (% Male)	89.9	56.0

# Disease Characteristics of 298 Matched HIV+ Adults

Est. Duration of Infection (yrs)	16.3 (9.7)
% AIDS	60.1% (179)
%cART	91.9% (274)
% with Detectable Virus	17.1% (51)
Nadir CD4	180 (37, 303)
Current CD4	569 (367, 798)
Beck Depression Inventory (BDI-II)	10.9 (9.8)
% Lifetime Depression	57.2% (170)
% Lifetime Substance Use Disorders	68.7% (202)
% LT Any Substance Dx (ETOH not included)	53.5% (138)
% Employed	36.7% (97)
% Cognitively Impaired (GDS)	<b>43.2% (128)</b>
Cognitive Symptoms (PAOFI)	5.1 (6.4)
% IADL-Dependent	25.4% (72)

# Rates of Impairment % on NIHTB Fluid Cognition Measures

	<u>HIV-</u>	<u>HIV+</u>
DCCS <40	12	19
Flanker <40	10	25
List Sort <40	14	20
Pic Sequence Memory <40	13	20
Pattern Comparison <40	16	25
Fluid Summary <40	13	25
2+ Fluid Tests <40	16	34

# Associations with Global Deficit Score Impairment Status in HIV+ Sample

	Impaired (n=128)	Normal (n=168)	<i>p</i> value
NIHTB Fluid T	42.6 (10.2)	51.1 (10.7)	<0.0001
Total Cognitive Symptoms	6.1 (6.6)	4.3 (6.2)	0.03
IADL-Dependent Tasks	2.4(2.6)	1.7(2.2)	0.02
% Employed	23.0% (26)	47.0% (71)	<0.0001
Duration of Infection (yrs)	17.7 (9.6)	15.3 (9.7)	0.03
% with AIDS	68.0% (87)	54.2% (91)	0.02
% with Detectable Virus	18.0% (23)	16.1% (27)	0.67
Nadir CD4	128 (20, 267)	198 (51, 370)	0.01
Current CD4	500 (332, 732)	632 (422, 818)	0.004

Note:  $\geq$  90% of participants in both groups were on cART

# Associations with NIHTB Fluid Cognition Impairment Status ( $\geq 2$ tests) in HIV+ Sample

	Impaired (n=100)	Normal (n=198)	<i>p</i> value
Global Mean T (GS Battery)	42.6 (7.5)	48.7 (6.4)	<0.0001
Total Cognitive Symptoms	6.1 (7.1)	4.5 (6.0)	0.04
IADL-Dependent Tasks	2.3(2.6)	1.9(2.3)	0.19
% Employed	28.3% (26)	41.3% (71)	0.04
Duration of Infection (yrs)	16.6 (9.2)	16.2 (10.0)	0.75
% with AIDS	66.0% (66)	57.1% (113)	0.14
% with Detectable Virus	22.0% (22)	14.7% (29)	0.09
Nadir CD4	149 (16, 292)	193 (46, 350)	0.07
Current CD4	553 (321, 733)	609 (406, 810)	0.06

Note: > 90% of participants in both groups were on cART



# Self Report NIH Toolbox Emotion Battery for Adults

## Psychological Well-being

Positive Affect  
Life Satisfaction  
Meaning & Purpose

## Negative Affect

Fear /Anxiety  
Sadness/Depression  
Anger Affect  
Anger Hostility  
Perceived Stress

## Social Satisfaction

Friendship  
Emotional Support  
Instrumental Support  
Loneliness\*  
Perceived Rejection\*

\*Reverse Scored for Summary Measure

# Problematic NIHTB-Emotion Battery Results for HIV+ (Effect Sizes vs. Matched Controls)

## Negative Affect

Fear/Anxiety	.61
Summary	.27

## Psychological Well Being

Positive Affect	.47
Meaning & Purpose	.44
Life Satisfaction	.21
Summary	.23

## Social Satisfaction

Loneliness	.69
Support (Instrumental)	.62
Support (Emotional)	.52
Friendship	.46
Perceived Rejection	.26
Summary	.47

# Correlations of NIHTB Emotion Summary Scores with MOS and POMS variables

N=343	Negative Affect Summary T	Social Satisfaction Summary T	Psychological Well-Being Summary T
MOS-HIV - General Health	<b>-0.43*</b>	0.30	<b>0.47*</b>
- Mental Health	<b>-0.64*</b>	0.02	<b>0.62*</b>
- Physical Health	-0.37	0.11	0.36
Beck Depression (BDI-II)	<b>0.75*</b>	0.11	<b>-0.48*</b>
POMS - Total	<b>0.77*</b>	-0.08	<b>-0.58*</b>
- Anxiety	<b>0.75*</b>	-0.12	<b>-0.48*</b>
- Depression	<b>0.72*</b>	-0.18	<b>-0.53*</b>
- Vigor	<b>-0.49*</b>	0.15	<b>0.57*</b>
- Anger	<b>0.63*</b>	-0.10	<b>-0.36</b>
- Confusion	<b>0.71*</b>	-0.11	<b>-0.52*</b>
- Fatigue	<b>0.56*</b>	0.02	<b>-0.47*</b>

Note: POMS=Profile Of Mood States; MOS=Medical Outcomes Study

\*p < 0.0001



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# Correlations Between Toolbox and Gold Standard NC Tests in HIV+

	TB Fluid Composite (T)	TB Oral Reading (T)
Gold Standard Mean NP (T)	0.57**	0.28**
WRAT-4 Reading (T)	0.19*	0.70**

\*\*p<0.0001

\*p<0.003

# Fluid vs. Crystallized Abilities

## ❖ Fluid

- Dynamic thinking
  - problem solving
  - learn/recall
  - processing speed
  - New memory encoding
- Important for adapting to novel situations—like HNRP battery
- Peaks in early adulthood and decreases with older age
- Sensitive to brain injury
  
- 5 Toolbox Measures
  - Card sorting, Flanker inhibition, List sorting, Pattern comparison, and Picture sequence memory

# Fluid vs. Crystallized Abilities: Different developmental trajectories

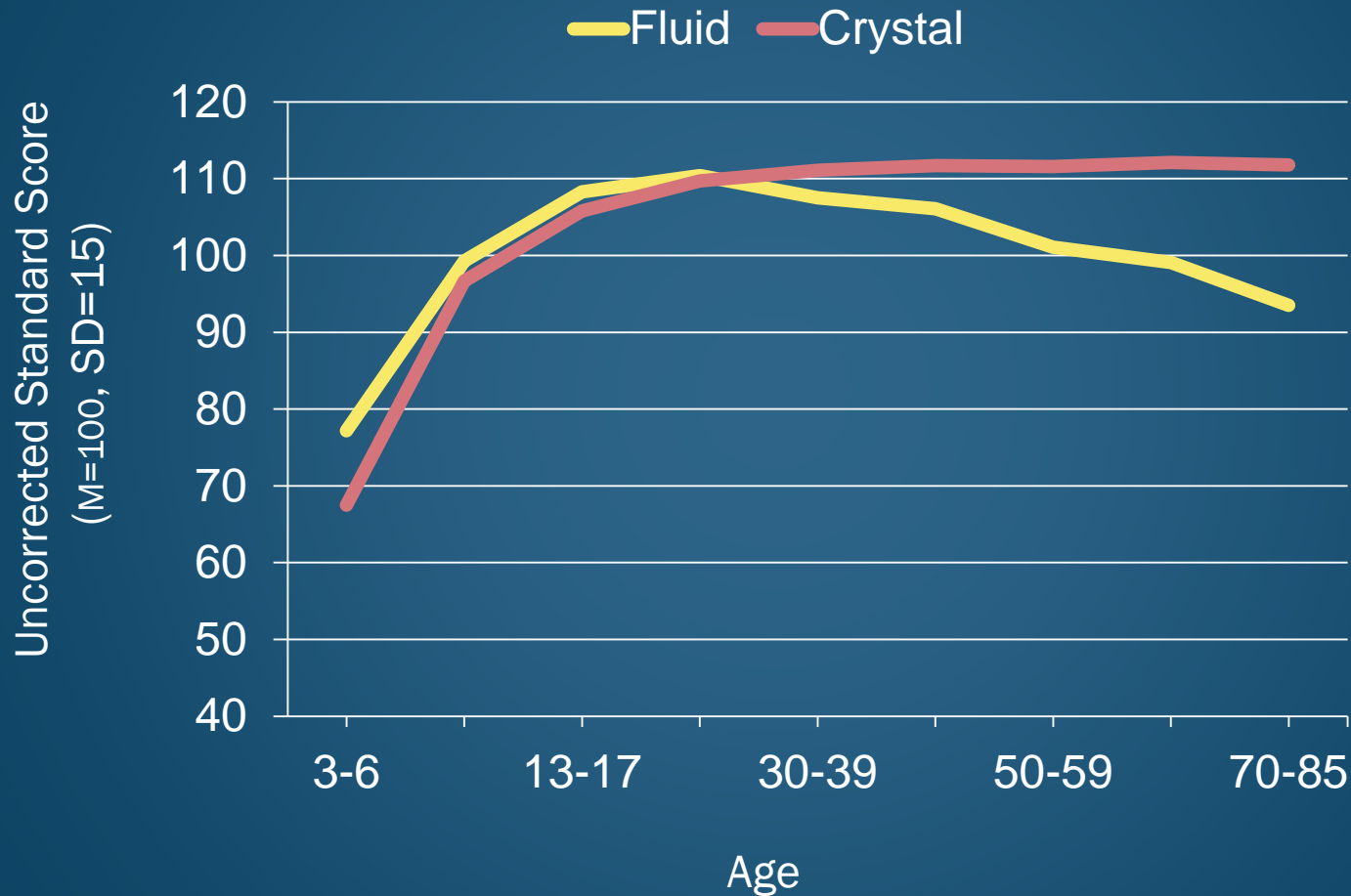


Figure: Casaletto et al. (2015) *JINS*.

# Crystallized vs. Fluid Abilities

- ❖ Crystallized
  - Accumulated store of learned verbal knowledge/skills
    - e.g., reading, vocab
  - Heavily influenced by culture and education & rapidly accumulated during childhood
  - Stabilizes (improves) with age (experience)
  - Not sensitive to brain injury (stable/“hold” abilities)
  
- 2 Toolbox Measures
  - Oral Reading and Picture Vocabulary



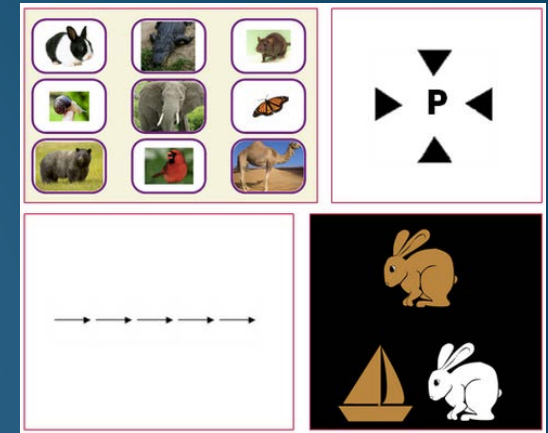
# NIH-TB Cognitive Battery Measures

	Test	Subdomain Measured	Description
Fluid	Dimensional Change Card Sort test (DCCS)	Executive Function/Shifting	Visual stimuli presented that must be matched to one of two images according to shape or color
	Flanker Inhibitory Control and Attention test (Flanker)	Executive Function	A central directional arrow is flanked by arrows on the left and right to test ability to inhibit attention to irrelevant task dimensions
	List Sorting Working Memory test (List Sort)	Working Memory	Series of images presented visually and verbally must be repeated orally in order of size, from smallest to biggest.
	Picture Sequence Memory (Picture Memory)	Episodic Memory	Pictured objects and activities presented must be placed in order in which they were presented as accurately as possible.
	Pattern Comparison Processing Speed test (Pattern Comparison)	Processing Speed	Identify whether or not two stimuli are the same
Crystallized	Oral Reading Recognition test (Reading)	Language (production)	Single words must be read aloud to measure ability to pronounce words.
	Picture Vocabulary test (Vocab)	Language (Comprehension)	Participant must match image to spoken word

<http://www.nihtoolbox.org/Pages/default.aspx>

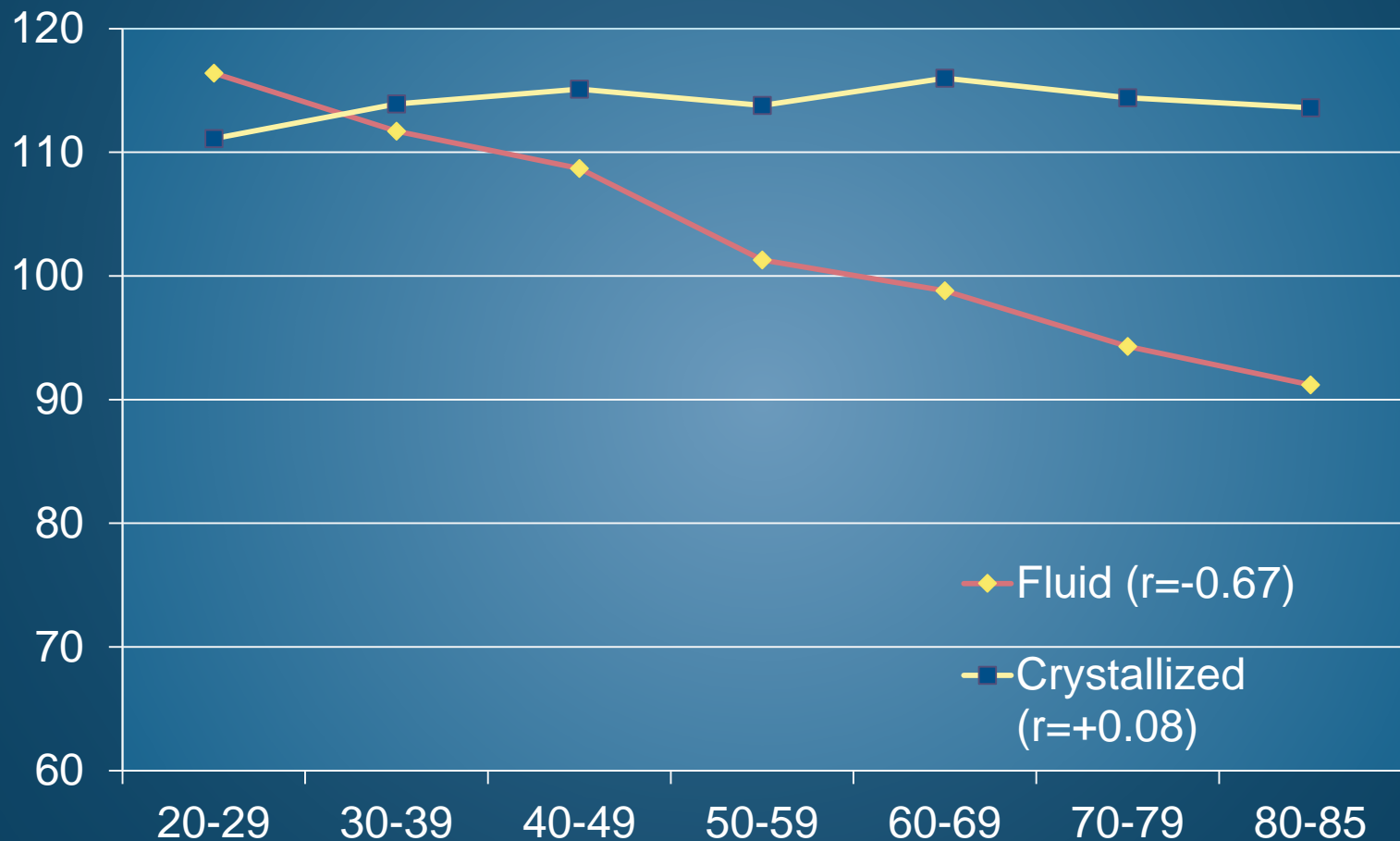
# NIH Toolbox Cognition Battery (NIHTB-CB)

- ❖ 1 of 4 batteries in the NIH Toolbox initiative
  - 1) Cognition, 2) Motor, 3) Sensation, & 4) Emotion
- ❖ 6 cognitive ability areas assessed:
  - Fluid (20 minutes)
    - Executive Functions, Episodic Memory,
    - Processing Speed, Working Memory, & Attention
  - Crystallized (10 minutes)
    - Language (Reading & Vocabulary)
- ❖ Strong test-retest reliability (ICC range: 0.78 to 0.99)
- ❖ Good construct/ecological validity (e.g., vs. other cognitive tests, health status)



Weintraub et al., 2013, *Neurology*; Heaton et al., 2014, *JINS*

# Age Effect on NIH Toolbox Cognition Composites in Adults



# Crystallized vs. Fluid Abilities

## ❖ Crystallized

- Accumulated store of verbal knowledge/skills
- Heavily influenced by culture and education & rapidly accumulated during childhood
- 2 Toolbox Measures
  - Oral Reading and Picture Vocabulary

## ❖ Fluid – dynamic, online processing

- Solve problems, think/act quickly, encode new memories
- Important for adapting to novel situations—like Gold Standard battery
- 5 Toolbox Measures
  - Card sorting, Flanker inhibition, List sorting, Pattern comparison, and Picture sequence memory



Different developmental trajectories

# Associations with Global Deficit Score Impairment Status in HIV+ Sample

	Impaired (n=128)	Normal (n=168)	<i>p</i> value
NIHTB Crystallized T	51.4 (8.7)	58.2 (8.8)	<0.0001
Total PAOFI Symptoms	6.1 (6.6)	4.3 (6.2)	0.032
% IADL-Dependent	29.5% (36)	22.2% (36)	0.16
% Employed	23.0% (26)	47.0% (71)	<0.0001
Duration of Infection (yrs)	17.7 (9.6)	15.3 (9.7)	0.032
% with AIDS	68.0% (87)	54.2% (91)	0.016
% with Detectable Virus	18.0% (23)	16.1% (27)	0.67
Nadir CD4	128 (20, 267)	198 (51, 370)	0.013
Current CD4	500 (332, 732)	632 (422, 818)	0.0043

Note:  $\geq$  90% of participants in both groups were on ART

# Construct Validity of NIHTB-Emotion Battery in HIV Infection: Correlations with Beck Depression Inventory-II (BDI-II) and Profile of Mood States

**Can't do bc only 58 ppl with emotions in matched cognition**

	Toolbox Negative Affect	Toolbox Social Satisfaction	Toolbox Psychological Well Being
Depression (BDI-II)	.76	*	-.65
POMS - Total	.79	*	-.54
- Anxiety	.77	-.21	-.45
- Depression	.75	*	-.52
- Anger	.66	*	-.32
- Confusion	.75	*	-.50
- Fatigue	.56	*	-.41
- Vigor	-.42	*	.49

\* < .20

# Associations with NIHTB Fluid Cognition Impairment Status ( $\geq 2$ tests) in HIV+ Sample

	Impaired (n=100)	Normal (n=198)	p value
Global Mean T (GS Battery)	42.57 (7.52)	48.72 (6.43)	<0.0001
Total PAOFI Symptoms	6.10 (7.11)	4.53 (5.99)	0.037
% IADL-Dependent	28.87% (28)	25.53% (44)	0.33
% Employed	28.26% (26)	41.28% (71)	0.037
Duration of Infection (yrs)	16.56 (9.21)	16.19 (9.97)	0.75
% with AIDS	66.00% (66)	57.07% (113)	0.14
% with Detectable Virus	22.00% (22)	14.65% (29)	0.095
Nadir CD4	149 (16, 292)	193 (46, 350)	0.069
Current CD4	553 (321, 733)	609 (406, 810)	0.064

Note: > 90% of participants in both groups were on ART

# Frascati Functional Impairment Criteria (Need 2)

1. Self report of IADL dependence, after person became HIV+
2. Self report of unable to work, or significantly reduced work efficiency
3. Self report of increased cognitive difficulties in everyday life (cannot use this if person has clinically significant depression),
4. Impaired performance on objective everyday functioning tasks: standardized work samples, medication management, financial management, driving simulators, etc.