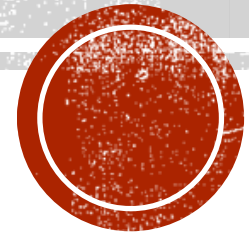


# **Exploring the Association Between the Route of HIV Acquisition and the Different Patterns of Neurocognitive Impairment**

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# DISCLOSURES

I have read and understood ICMJE policy on declaration of interest and I declare that I have no conflicting interest

In the past five years I received:

- research grants from Gilead, Viiv and BMS;
- speaker's honoraria from Abbvie, BMS, Gilead, Janssen-Cilag, MSD, Viiv.



## BACKGROUND

- The **prevalence of HIV-Associated Neurocognitive Disorders (HAND)** is currently estimated at **20–50%**
- HIV-infected individuals suffering from asymptomatic HAND (**ANI**) were found to have the largest deficits in **language and verbal functions**, while individuals with symptomatic HIV (**MND**) and AIDS (**HAD**) were found to have the greatest deficits in **motor and executive functioning**. As HIV disease progresses, motor functioning, executive skills, and speed of information processing demonstrate the greatest decline

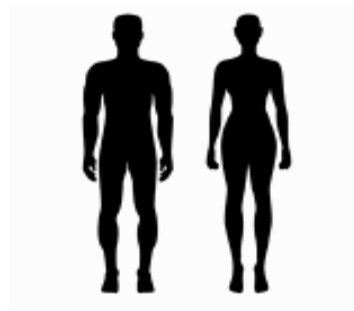


- HAND itself can lead to detrimental behaviors such as poor adherence and increased HIV transmission behaviors. In turn, poor adherence and many of the risk factors for HIV acquisition (mental illness, substance abuse, STI) can trigger HAND. In order to effectively reduce the transmission/progression of HIV, as well as to better define HAND as a target for diagnostic and therapeutic tools, it is necessary to **better understand the complex reciprocal relationship between HAND and HIV risk factors**



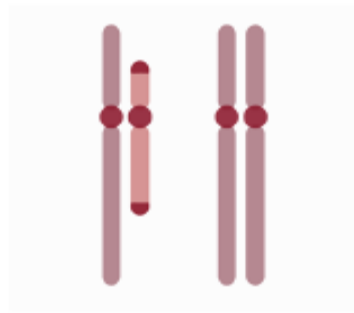
# BACKGROUND (A SEXIST EXAMPLE)

- Most of these risk factors can be clustered together according to HIV acquisition routes (ARs)
- ARs underlie several factors able to affect viroimmunological and neurocognitive status:
  - Gender and Sex
  - Coinfections
  - Drugs and Alcohol assumption
  - Comorbidities (CV risk)
  - Social background (education, employment)
  - cART regimens and adherence
  - Clinical stage at HIV diagnosis...



## Anatomic Differences:

- Acquisition sites: female genital tract versus rectal mucosa
- Hormonal modulation of risk at the female genital tract
- Drug penetration to mucosal sites



## Genetic differences:

- Gene dosage effects of X chromosome encoded genes/incomplete X inactivation
- Regulatory function of X-encoded microRNAs
- Estrogen responsive elements in promoters of multiple immune active genes



## Immune cell phenotypes:

- Higher interferon alpha production from plasmacytoid dendritic cells from women
- Sex differences in the efficacy of vaccines
- Hormone modulation of immune cell function



## Microbiome:

- Female genital tract and rectal mucosa with distinct microbiome compositions that determine local inflammation and acquisition risk
- Direct effects of the vaginal microbiome on local antiretroviral drug levels
- Sex hormone modulation of the gut microbiota that contributes to systemic inflammation

## Latency maintenance:

- Estrogen blockade of HIV transcriptional activation
- Sex specific epigenetic modifications in immune cells



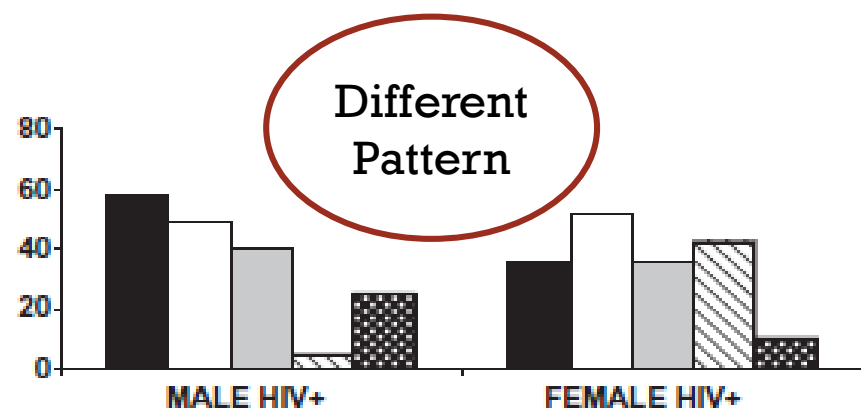


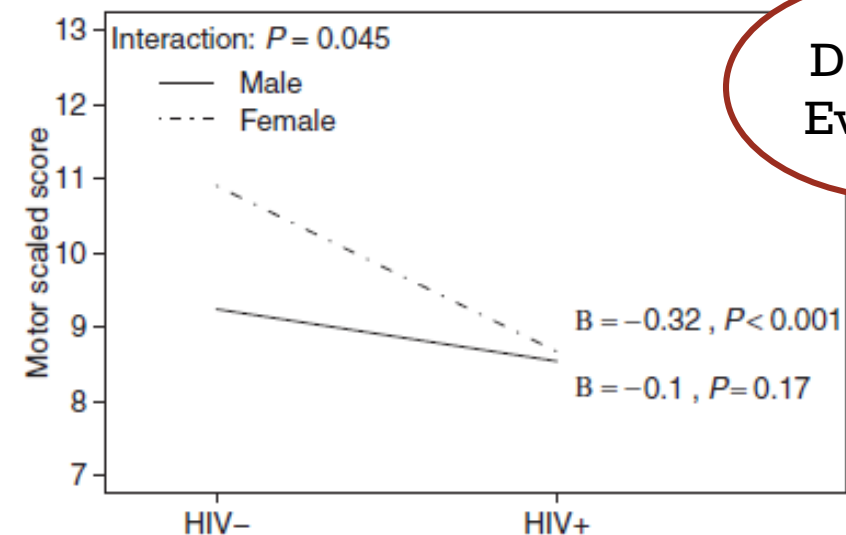
Figure 2. Type of impairment. ■ Visual memory; □ Attention/Psychomotor speed; ▒ Abstract reasoning/Verbal intelligence; ▤ Verbal memory for texts; ▦ Verbal memory for digits and words.

	Women			Men		
	HIV+	HIV-	Cohen's d	HIV+	HIV-	Cohen's d
Letter fluency	-0.9673	-0.0256	-0.95**	0.2493	0.0351	0.22
Animal fluency	-1.1487	0.0697	-0.94**	0.2776	-0.0912	0.36
Action fluency	-0.9486	0.1552	-1.20****	-0.2381	-0.2060	-0.31
Digit symbol	-0.9852	0.1996	-1.42*****	-0.3440	-0.2656	-0.08
Symbol search	-1.0076	0.2031	-1.30*****	-0.0336	-0.2704	0.23
Trails A	-1.3375	0.1838	-1.38*****	-0.1302	-0.2523	0.13
Color trails 1	-0.9648	0.2371	-1.02***	-0.2085	-0.3158	0.09
Stroop Word	-0.6928	0.2501	-0.88*	-0.2858	-0.3758	0.11
Stroop Color	-0.9212	0.3921	-1.43*****	-0.2096	-0.5314	0.39
Stroop Color-Word	-0.5289	0.2977	-1.00**	-0.1025	-0.4282	0.44
PASAT 50	-0.6905	0.2773	-1.05**	0.4106	-0.3537	0.66
Spatial span	-0.7960	0.0730	-0.79	0.0730	-0.0986	0.14
Category test	-0.8237	0.0515	-0.94*	-0.1378	-0.0741	-0.06
WCST-64	-0.3301	0.0066	-0.28	0.0412	-0.0086	0.06
Color trails 2	-0.7736	0.2756	-0.93*****	0.1393	-0.3675	0.50
BVMT Learning	-0.3517	0.2561	-0.56	0.4613	-0.3413	0.80
BVMT Delay	-0.3463	0.2241	-0.46	0.4377	-0.2962	0.80
HVLT Learning	-0.6924	0.0679	-0.74	0.2138	-0.0912	0.32
HVLT Delay	-0.9969	0.0898	-0.97*	-0.1287	-0.1155	-0.02
Pegs Dominant	-0.0530	0.1441	-0.47	-0.1964	0.1922	-0.30
Pegs Nondominant	-0.0909	0.1630	-0.57	-0.3112	-0.2177	-0.07

## BACKGROUND

Model	Association between sex (women versus men) and the odds of NCI	
	OR (95% CI)	P
Step 1: Adjusted for relevant covariates	1.53 (1.13–2.06)	0.005
Step 2: Adjusted for relevant covariates and individual biopsychosocial risk factors		
Low reading level	1.19 (0.87–1.63)	0.29
Low education	1.50 (1.11–2.03)	0.009
Depressed mood	1.49 (1.10–2.01)	0.01
LT SUD	1.50 (1.11–2.02)	0.009
Alcohol	1.53 (1.13–2.07)	0.005
Cocaine	1.55 (1.15–2.09)	0.004
Methamphetamine	1.51 (1.11–2.04)	0.008
Opiates	1.56 (1.16–2.11)	0.004
Syndemics count	1.38 (1.02–1.87)	0.04

Different Risk



Different Evolution

## **THE AIM**

**To define whether ARs may affect HAND phenotype and thereby the neurocognitive screening tests (NC-STs) performance**



# METHODS

- **Observational, Cross-sectional and Diagnostic accuracy** (STARD Guidelines 2015) study
- **Inclusion criteria:**
  - Age >18 years
  - WB confirmed HIV-positivity
  - Being on cART
  - Length of HIV infection > 6 months
- **Exclusion criteria:**
  - Opportunistic infections, infective, neoplastic, traumatic, vascular or neurodegenerative CNS disorders
  - Active drug or alcohol abuse (within 6 months apart)
  - A Beck depression inventory-II score  $\geq 30$
  - An Hamilton Anxiety Rating Scale-A  $\geq 25$
  - Language barriers
- Patients were grouped according to self-reported ARs: **males who have sex with males (MSM)**, **previous intravenous drugs users (pIDU)** and **heterosexuals (HS)**; comparisons were performed through non parametric tests (t-test, chi-squared test, ANOVA)



## METHODS

- **Index tests:** IHDS (range: 0-12; cut-off  $\leq 10$  abnormal) – Italian adaptation of MACE (range: 0-30; exploratory cut-offs) – **Gold standard:** Complete neurocognitive evaluation (NE)

Domain	Test*
<b>Memory</b>	Disyllabic Words Serial Repetition – Digit span forward – Corsi block-tapping – Free and Cued Selective Reminding [Immediate and Delayed Recall] – Sens Cues Sensitivity – Story Recall – Rey-Osterrieth complex figure [Delayed Recall]
<b>Attention/Working Memory</b>	Trail Making part B – Stroop Colour [Reaction times and Errors] – Digit Span backward
<b>Executive Functions</b>	Frontal Assessment battery – Phonemic Verbal fluency
<b>Processing Speed</b>	Digit Symbol – Trail Making part A and B-A
<b>Visuospatial Construction</b>	Rey-Osterrieth complex figure [Copy]
<b>Motor Functioning</b>	Groove Pegboard test for dominant/non dominant hand

*\*All tests' scores were age/education-normalized*

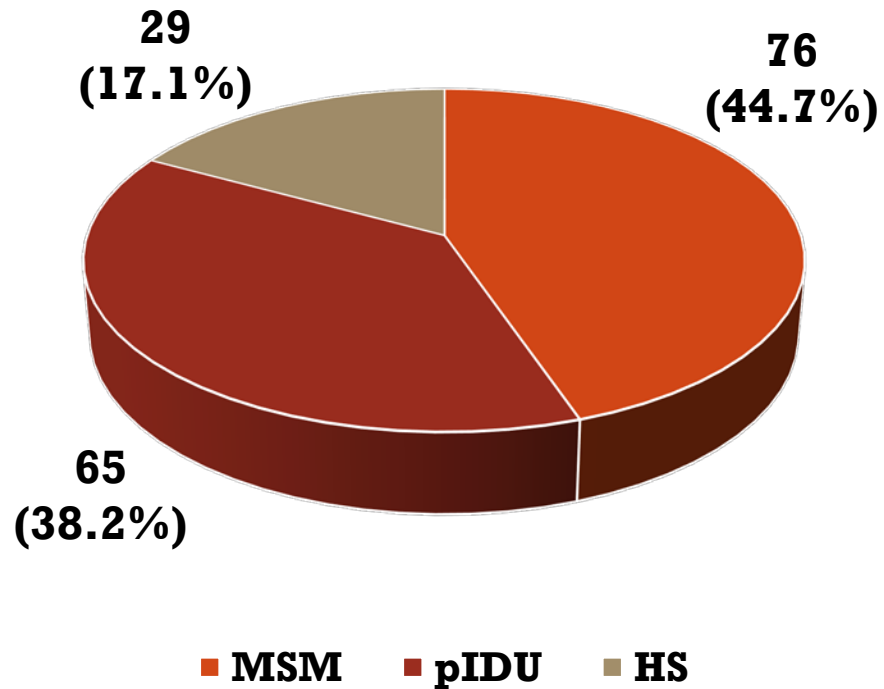
- **Instrumental Assessment of Daily Living (IADL)** was applied for functional impairment to differentiate between ANI and symptomatic HAND, according to **Frascati's criteria** (2007)
- Diagnostic accuracy, inter-rater reliability and clinical utility analysis were performed for both IHDS and MACE in the groups





# POPULATION

Acquisition Routes, n 170



Parameters	MSM (n=76)	IDU (n=65)	HS (n=29)	p
Age, years	52 (46-59)	54 (51-57)	53 (47-61)	.310
Male Sex, n	76 (100%)	42 (64.6%)	12 (41.4%)	<.01
Education, years	12 (8-13)	8 (8-11)	8 (8-8)	<.01
Caucasian ethnicity, n	75 (98.7%)	64 (98.5%)	27 (93.1%)	.243
Hepatitis coinfection, n	6 (7.9%)	42 (64.6%)	0 (0%)	<.01
Current CD4 count, cell/uL	598 (448-849)	523 (408-833)	536 (403-692)	.386
Nadir CD4, cell/uL	207 (103-314)	208 (145-328)	117 (54-300)	.369
PI viremia <50 cp/mL, n	70 (92.1%)	57 (87.7%)	26 (89.6%)	.664
PI HIV-RNA, Log10 cp/mL	0.04 (0.04-1.3)	1.3 (0.04-1.3)	0.04 (0.04-1.2)	.050
cART regimen, n				.362
PI-based	15 (19.7%)	12 (18.5%)	2 (6.9%)	
INI-based	20 (26.3%)	24 (36.9%)	11 (37.9%)	
NNRTI-based	21 (27.6%)	8 (12.3%)	9 (31.0%)	
Others	20 (26.3%)	21 (32.3%)	7 (24.1%)	
CPE, score	6 (6-7)	7 (6-7)	7 (6-8)	.604



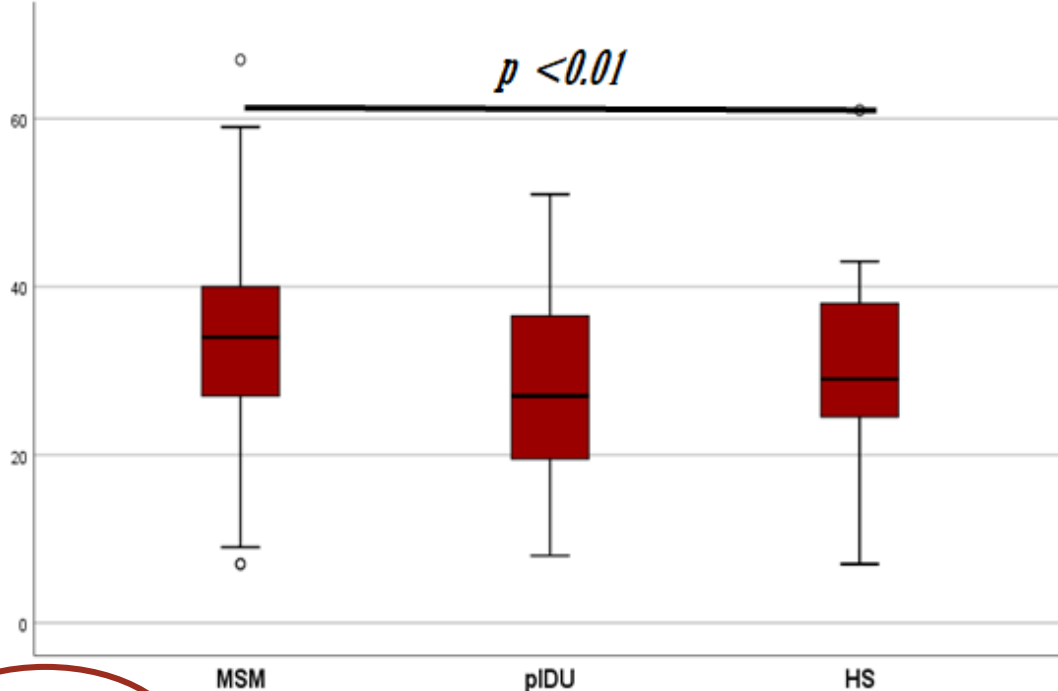
# NEUROCOGNITION

Parameters	MSM (n=76)	IDU (n=65)	HS (n=29)	<i>p</i>
<b>HAMA, score</b>	2 (1-4)	3 (2-8)	3 (1-7)	.173
<b>BDI-II, score</b>	3 (1-15)	6 (2-11)	3 (1-9)	<b>.033</b>
<b>HAND, n</b>	42 (55.3%)	47 (72.3%)	19 (65.5%)	.122
<b>ANI</b>	37 (48.7%)	38 (58.5%)	17 (58.6%)	.442
<b>MND</b>	5 (6.6%)	9 (13.8%)	2 (6.9%)	.433
<b>HAD</b>	0 (0%)	0 (0%)	0 (0%)	/
<b>Complainer, n</b>	46 (60.5%)	50 (78.1%)	16 (55.2%)	.066
<b>MACE, score</b>	27 (23-30)	23 (19-26)	27 (23-29)	<b>&lt;.01</b>
<b>Altered MACE (≤26), n</b>	27/55 (49.1%)	35/44 (79.5%)	9/22 (40.9%)	<b>&lt;.01</b>
<b>IHDS, score</b>	10.5 (9-11)	9.5 (8-11)	10 (9-10.5)	<b>&lt;.01</b>
<b>Altered IHDS (≤10), n</b>	34 (44.7%)	44 (67.7%)	21 (72.4%)	<b>&lt;.01</b>

Statistically  
relevant –  
Clinically  
relevant?

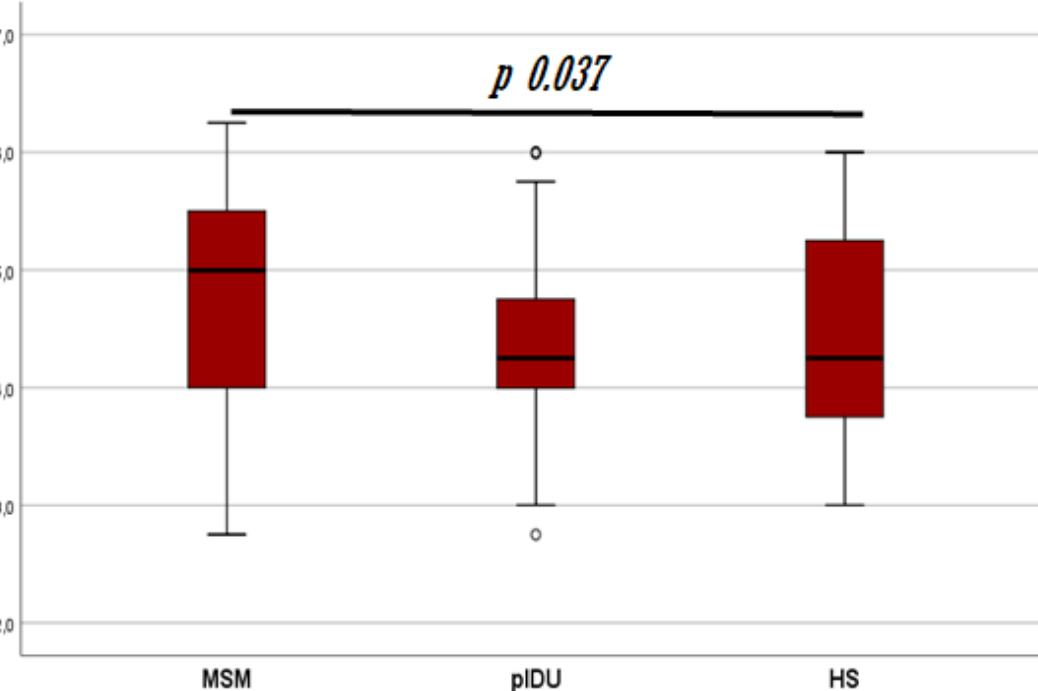


*Age/Education-adjusted Symbol Digit Modalities test score*



Processing  
Speed

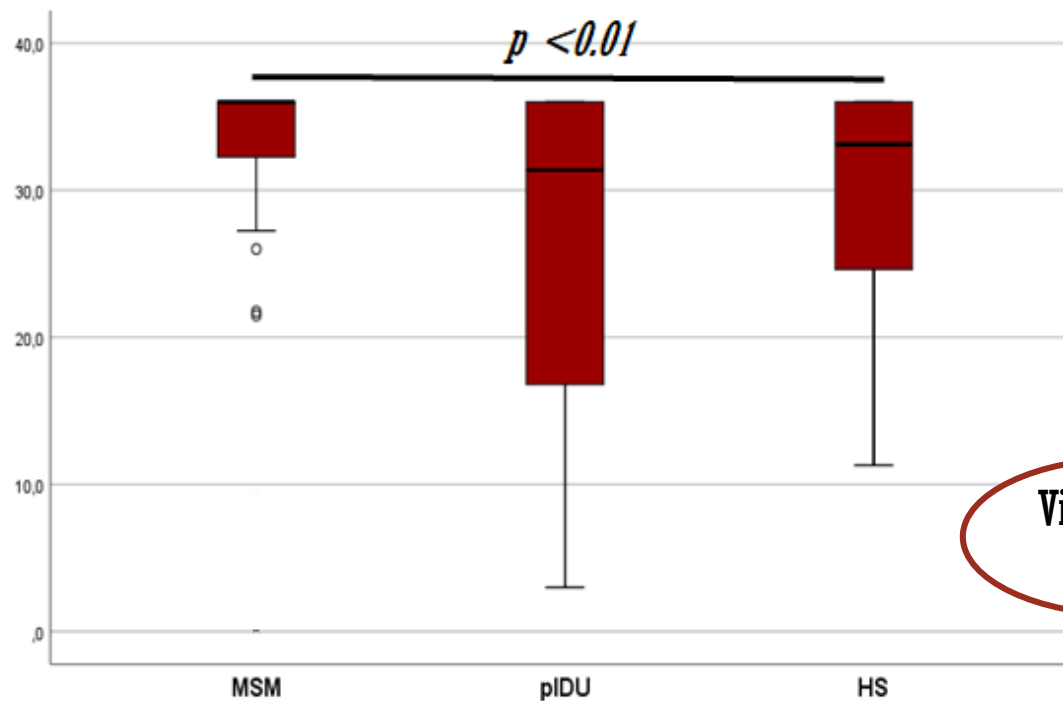
*Age/Education-adjusted Corsi test score*



Visuospatial short-  
term working memory

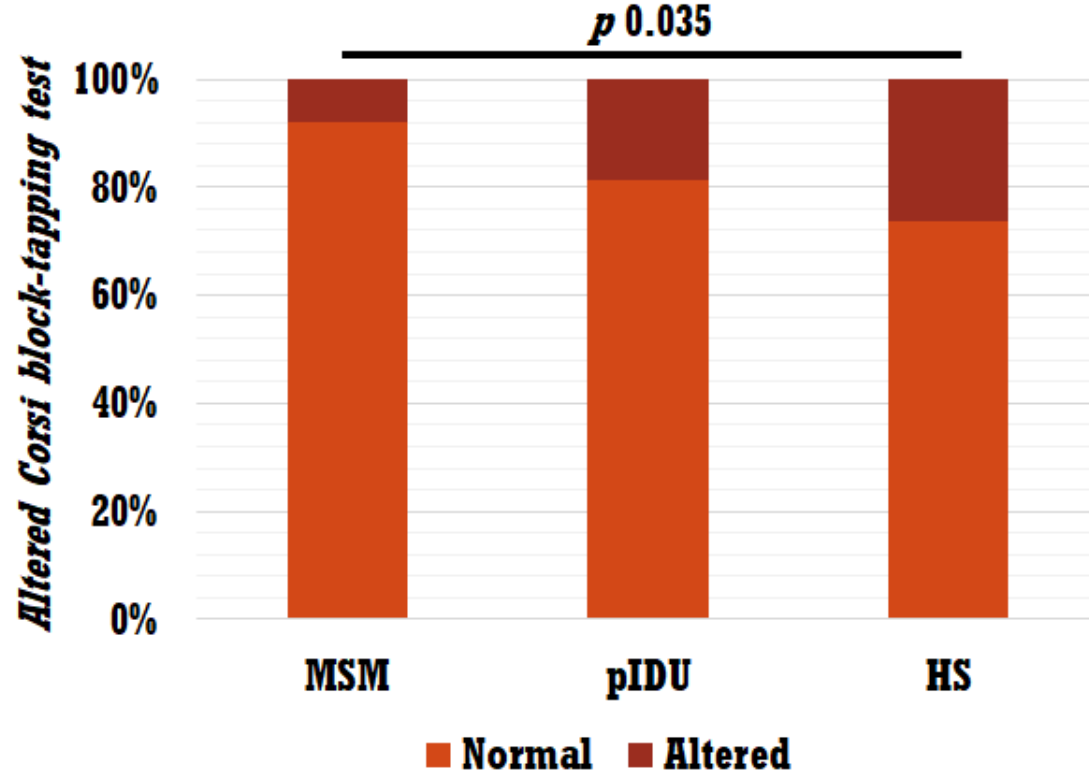
## NEUROCOGNITIVE PERFORMANCE

*Age/Education-adjusted Rey-Osterrieth complex figure Copy score*

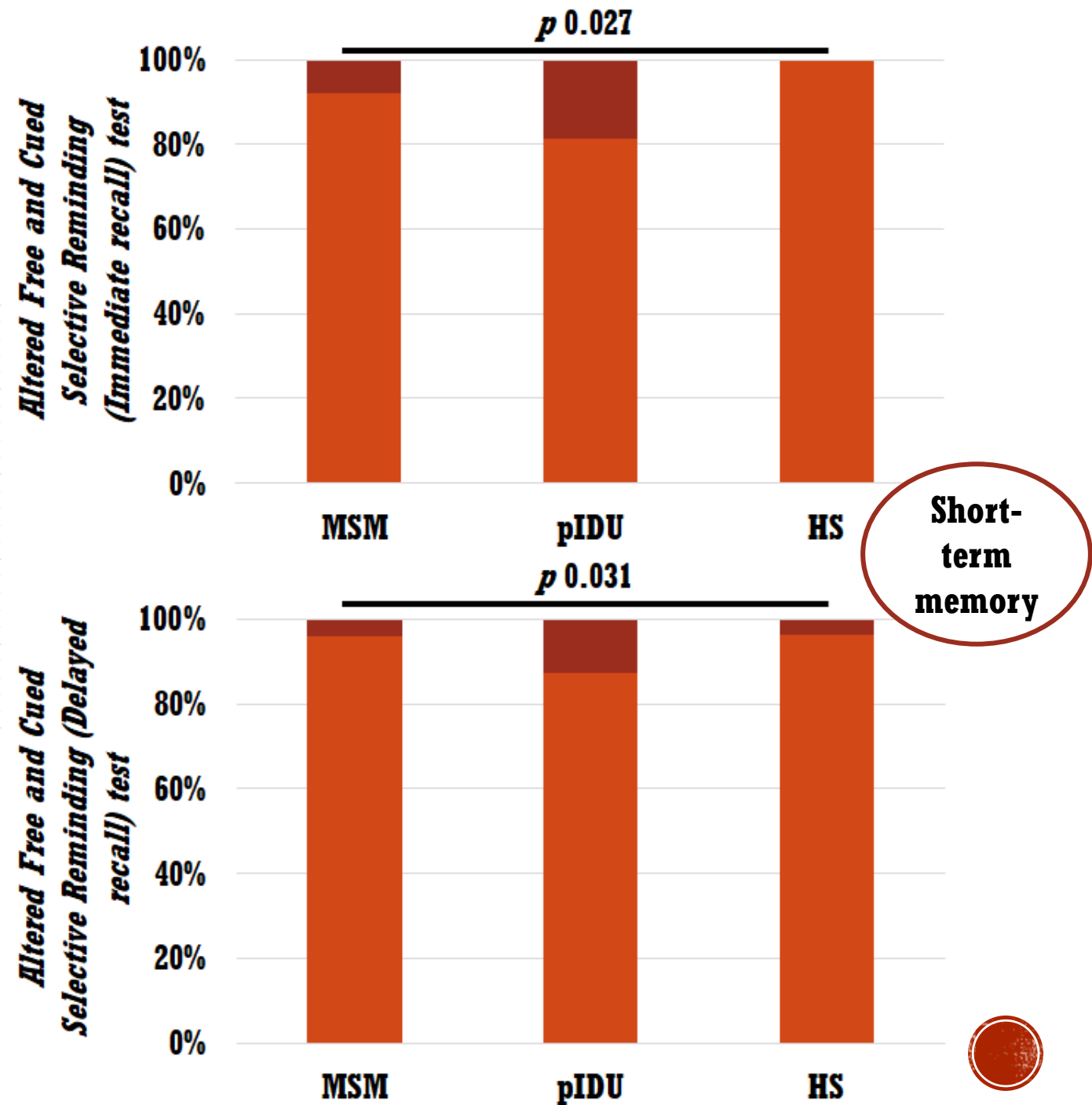


Visuospatial  
abilities

# NEUROCOGNITIVE PERFORMANCE



Visuospatial  
short-term  
working memory





## SCREENING: Diagnostic Accuracy & Clinical Utility

ARs	NC-ST	Sensitivity	Specificity	PPV	NPV	YJ	LR+	LR-	CCR
Overall	MACE≤26	84.8%	66.7%	82.7%	70.0%	0.51	2.5	0.2	78.5%
	IHDS≤10	71.2%	64.5%	77.8%	56.3%	0.36	2.0	0.4	68.8%
MSM	MACE≤26	80.6%	91.7%	92.6%	78.6%	0.72	9.7	0.2	85.4%
	IHDS≤10	61.9%	76.5%	76.5%	61.9%	0.38	2.6	0.5	68.4%
pIDU	MACE≤26	90.9%	54.5%	85.7%	66.7%	0.45	2.0	0.2	81.8%
	IHDS≤10	76.6%	55.5%	81.8%	47.6%	0.32	1.7	0.4	70.8%
HS	MACE≤26	53.3%	85.7%	88.8%	46.1%	0.39	3.7	0.5	63.6%
	IHDS≤10	78.9%	40.0%	65.5%	71.4%	0.19	1.3	0.5	65.5%

## SCREENING: Inter-Rater Agreement

ARs	NC-ST	Cohen's k	Agreement with Gold Standard
MSM	MACE	0.71	Good
	IHDS	0.37	Poor
pIDU	MACE	0.48	Moderate
	IHDS	0.31	Poor
HS	MACE	0.31	Poor
	IHDS	0.19	Very Poor

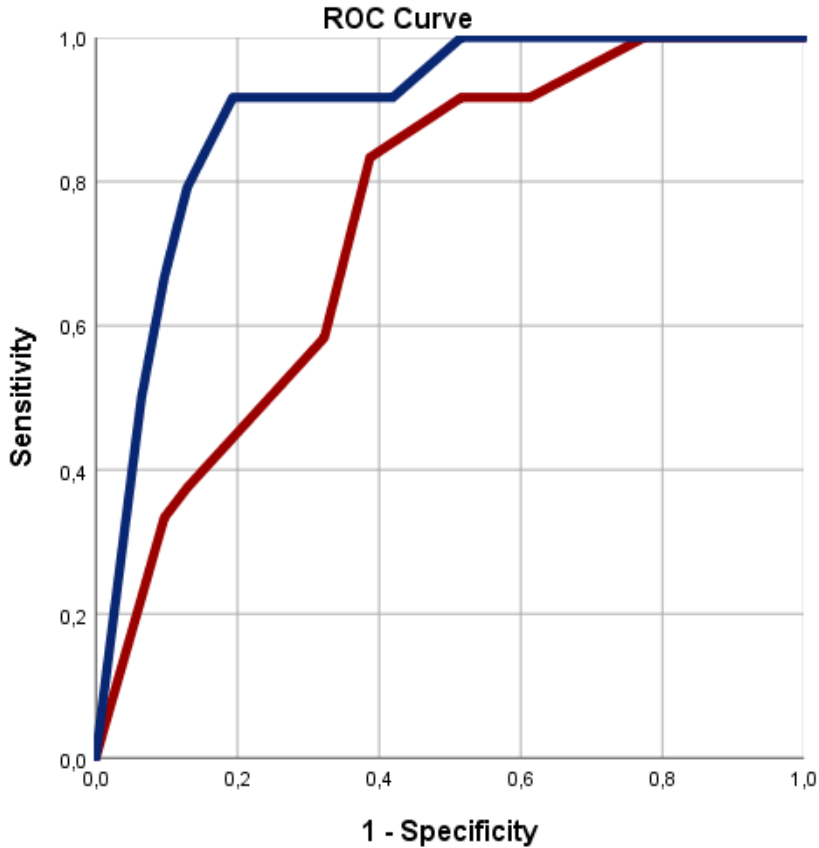
 Best performance  
 Worst performance





# ROC ANALYSIS

**MSM**

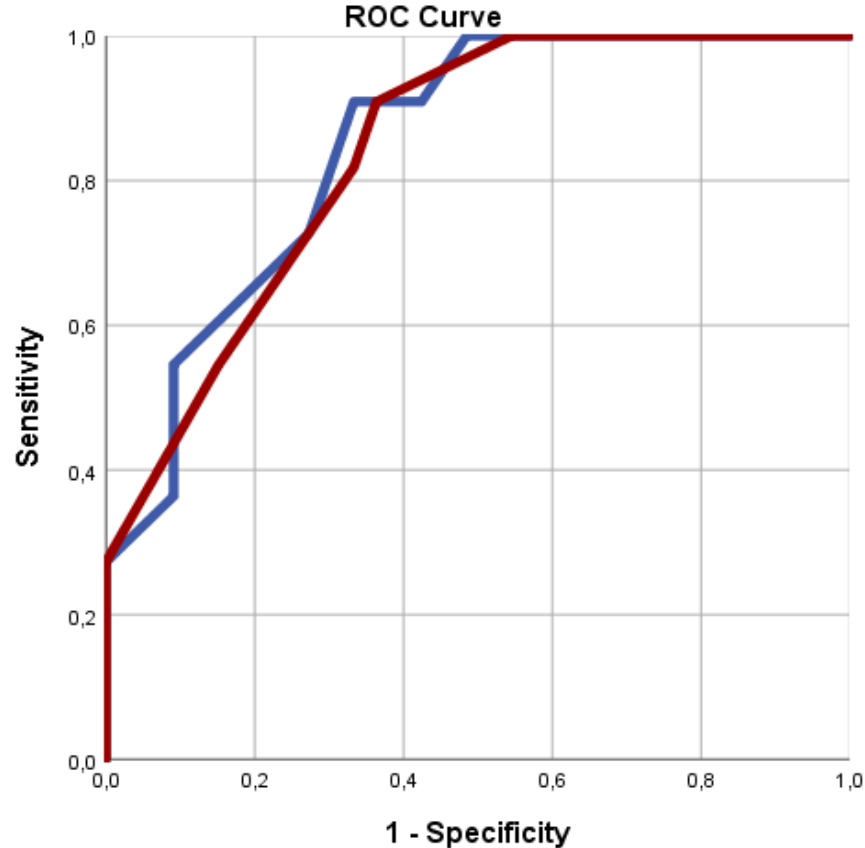


**MACE AUROC: 0.89 (0.81-0.98; p <.01)**

**IHDS AUROC: 0.74 (0.62-0.87; p<.01)**

**MACE better**

**pIDU**

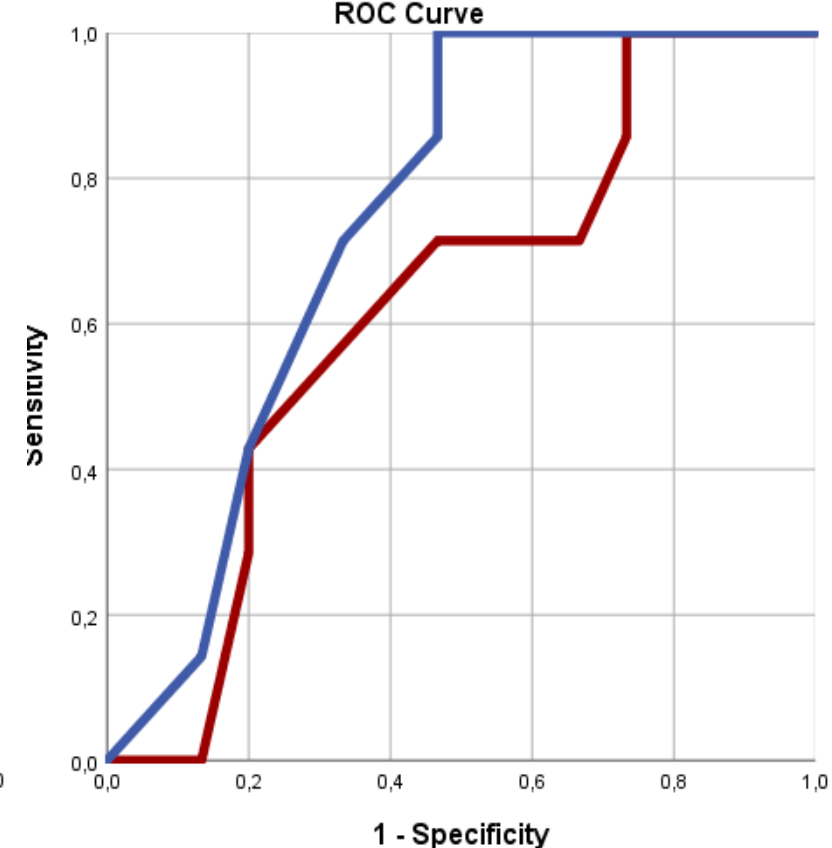


**MACE AUROC: 0.85 (0.73-0.97; p <.01)**

**IHDS AUROC: 0.84 (0.72-0.96; p<.01)**

**Both equally good**

**HS**



**MACE AUROC: 0.74 (0.54-0.95; p 0.07)**

**IHDS AUROC: 0.62 (0.38-0.87; p 0.36)**

**Both poor – IHDS worst**



## **LIMITATIONS**

- **Observational study**
- **Limited sample size**
- **Ongoing multivariate and covariate analyses**
- **Ongoing record of data regarding other coinfections and history of treatment and HIV infection**
- **Comparative/diagnostic (inter-rater agreement) bias related to the pre-determined neurocognitive battery**



## DISCUSSION

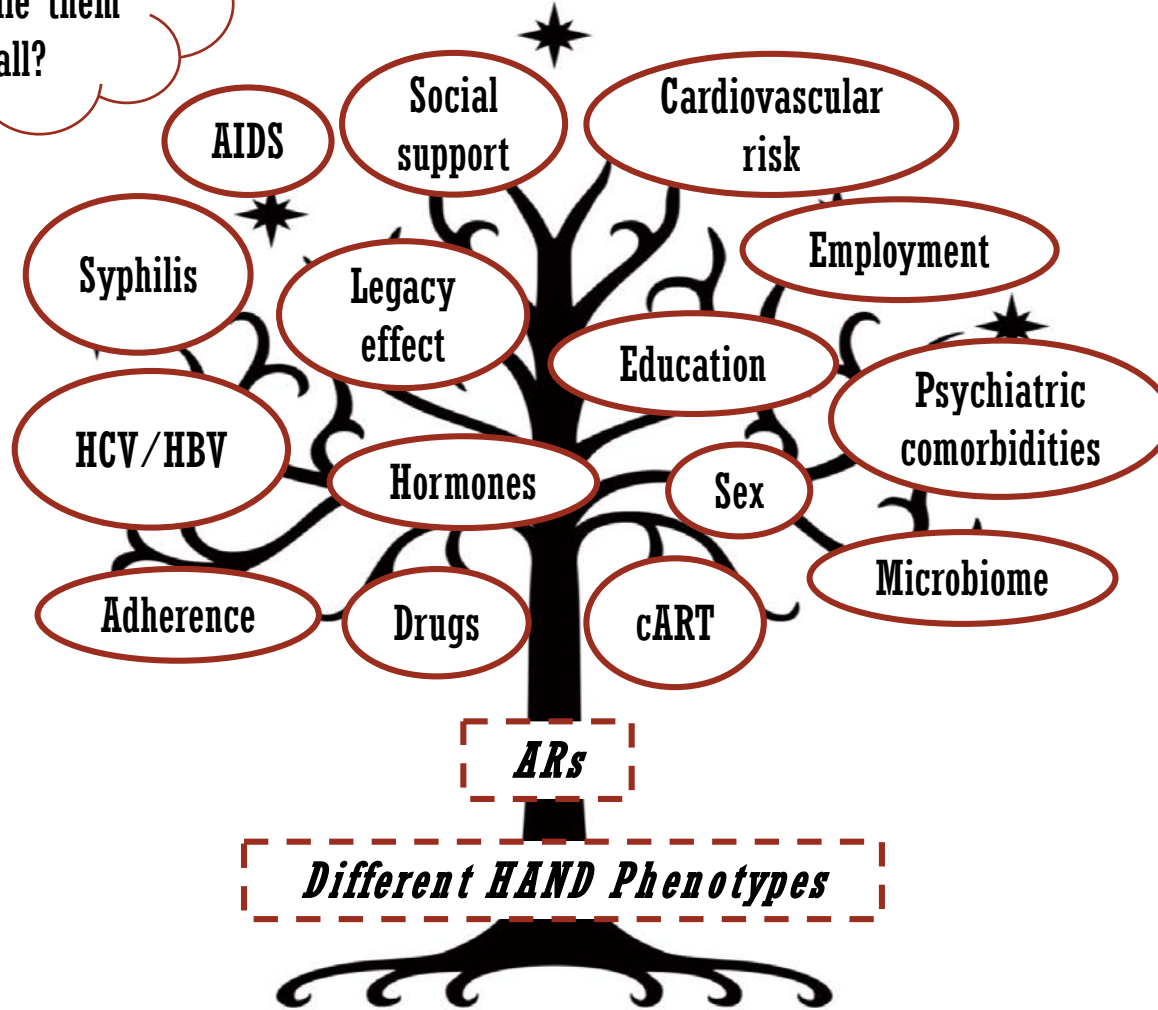
- In our population, despite similar prevalence of HAND and its severity distribution between MSM, pIDU and HS, these **ARs differed in several factors that may affect HAND prevalence and phenotype**: HCV-coinfection, Sex, History of Drug abuse, and Education (Depression)
- **HAND phenotypes differed according to ARs**; compared to MSM, pIDU and HS presented variably reduced abilities in:
  - Processing speed
  - Visuospatial construction
  - Visuospatial short-term working memory
  - Short-term memory adjusted for attention/learning deficits
- **This difference may affect the diagnostic accuracy and clinical utility of HAND screening tools**; in fact, MACE and IHDS performed similarly and effectively in screening pIDU, both poorly HS, while MACE was more accurate than IHDS in MSM





One Screening  
to Rule them  
all?

## CONCLUSION



Variable Accuracy of  
Neurocognitive battery according to  
tests' combinations and Screenings  
between ARs



Probably  
not this  
time

Need of a better  
characterisation of HAND  
phenotype according to  
clinical and demographic  
clusters of variables in  
order to improve HAND  
detection