Istituto Nazionale per le Malattie Infettive "Lazzaro Spallanzani"
Istituto di Ricovero e Cura a Carattere Scientifico

Approccio al paziente tossicodipendente con infezioni virali croniche

Mauro Zaccarelli

INMI Spallanzani, IRCCS

Table 4. Opiate-induced immune function modulation *in vivo* and *in vitro*

Mode of administration	Immune function	Activity
In vivo		
Rodents	Phagocytosis	Decreased
	Antibody production	Decreased
	Mitogen proliferation	Decreased
	NK/CTL activity	Decreased
	Cytokine production	Decreased
	Cytokine levels	Increased
	LPS-induced sepsis	Increased
	Cutaneous hypersensitivity	Decreased
Humans	Phagocytosis	Decreased
	NK activity	Decreased
	Cell cytotoxicity	Decreased
Monkeys	Chemotaxis	Decreased
	PMN killing	Decreased
Pigs	Cutaneous hypersensitivity	Decreased
In vitro		
Mice	Phagocytosis	Decreased
	Cell proliferation	Decreased
	Antibody production	Decreased
	Cytokine production	Decreased
	Chemotaxis	Decreased
	Superoxide production	Decreased
	Cytokine production	Variable
	Chemokine production	Variable

CTL, cytotoxic lymphocytes; PMN, polymorphonuclear.

Table 6. Cocaine-induced immune modulation

Mode of administration	Activity	Effect
In vivo		
Humans	Antimicrobial activity	Decreased
	Cytokine production	Variable
Rodents	Lymphocyte proliferation	Decreased
	Antibody formation	Decreased
	Cellular hypersensitivity	Decreased
	Th1/Th2 cells	Variable
	Cytokine production	Variable
In vitro		
Humans	HIV replication	Increased
	Lymphocyte proliferation	Decreased
	Cytokine production	Decreased
Rodents	Cytokine production	Decreased
	Lymphocyte proliferation	Decreased
	NK cell activity	Decreased

Friedman, FEMS Immunol Med Microbiol 2006

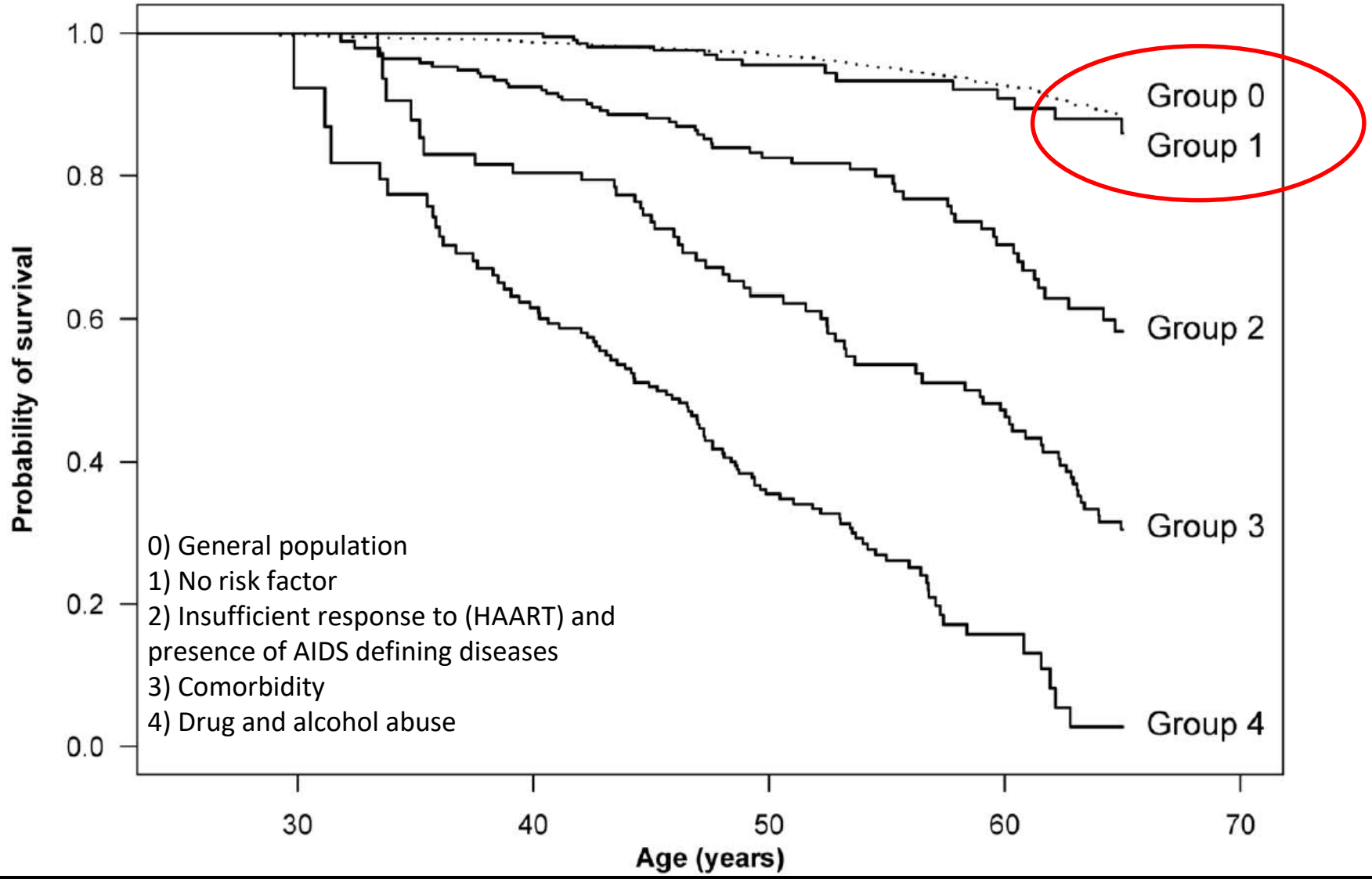
Infezione da HIV e TD

Survival after HIV Diagnosis by Transmission Category, 33 U.S. States, 1996-2004

		Probability of surviving 1 year after HIV Dx		Probablity of surviving 3 year after HIV Dx	
Tx Category	No	%	95% CI	%	95% CI
MSM	82,673	95.2	95.2 , 95.3	91.6	91.6 , 91.7
IDU Male	17,528	93.2	93.1 , 93.4	87.3	87.1 , 87.4
Female	9,498	95.1	95.0 , 95.3	89.5	89.4 , 89.6
MSM & IDU	7,616	95.5	95.5 , 95.6	90.7	90.6 , 90.8
HRH					
Male	18,670	95.7	95.6 , 95.8	91.9	91.8 , 91.9
Female	33,708	96.8	96.7 , 96.9	93.3	93.3 , 93.4

Grigoryan, APHA 2008

Impact of Non-HIV and HIV Risk Factors on Survival in HIV-Infected Patients on HAART: A Population-Based Nationwide Cohort Study (Denmark)

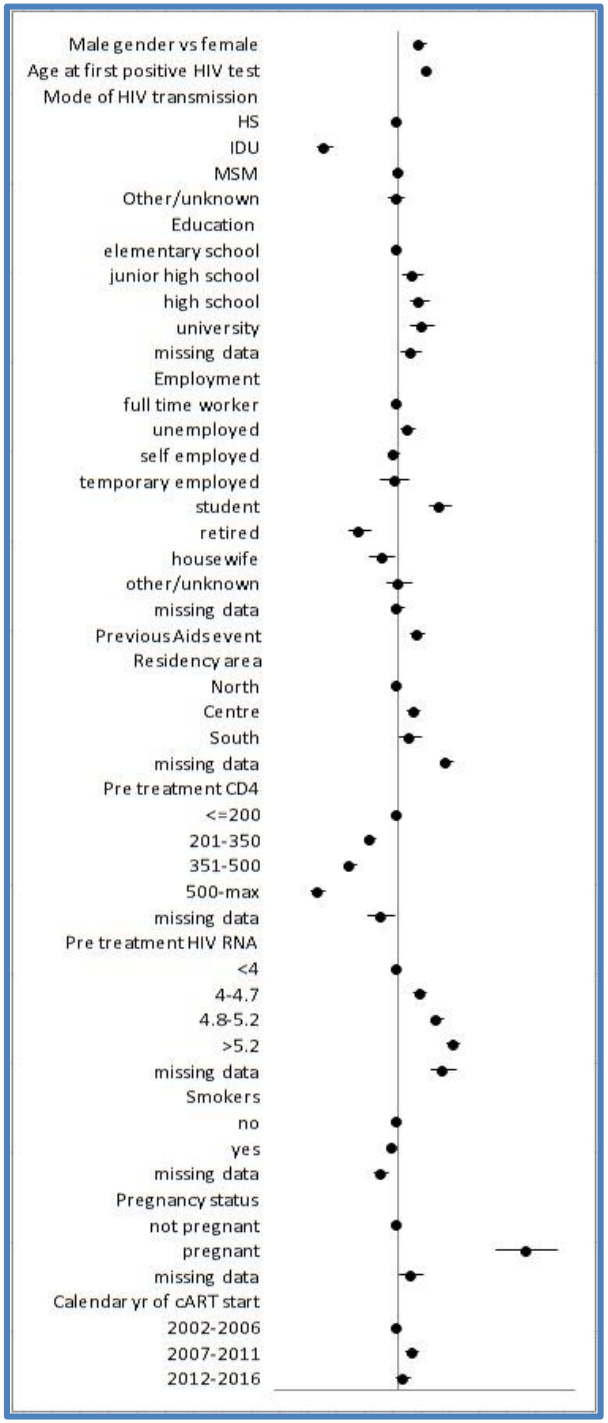


Obel, Plos One 2011

Results (1): ART initiation

Multivariable model of factors associated with time to ART initiation

- A total of **6,214 (77.5%) started ART** during the study period.



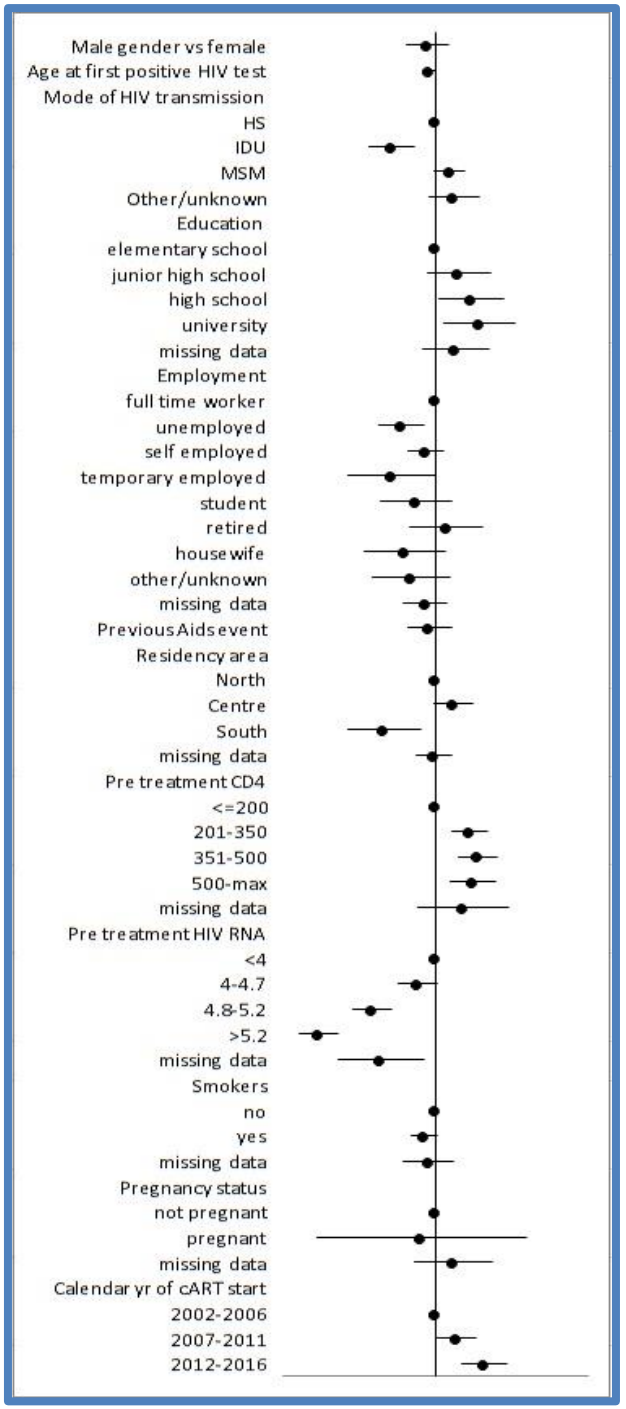
	HR (95% CI)	p-value
Male gender vs female	1.33 (1.22-1.45)	<0.001
Age at first positive HIV test	1.46 (1.42-1.50)	<0.001
Mode of HIV transmission		
HS	1.00	
IDU	0.39 (0.35-1.07)	<0.001
MSM	1.00 (0.94-1.07)	0.956
Other/unknown	0.99 (0.89-1.09)	0.792
Education		
elementary school	1.00	
junior high school	1.21 (1.06-1.38)	0.004
high school	1.33 (1.17-1.52)	<0.001
university	1.37 (1.18-1.59)	<0.001
missing data	1.19 (1.04-1.36)	0.012
Employment		
full time worker	1.00	
unemployed	1.15 (1.05-1.25)	0.002
self employed	0.94 (0.87-1.01)	0.107
temporary employed	0.96 (0.80-1.15)	0.660
student	1.74 (1.49-2.02)	<0.001
retired	0.61 (0.53-0.71)	<0.001
housewife	0.82 (0.69-0.97)	0.018
other/unknown	1.02 (0.87-1.20)	0.830
missing data	0.99 (0.91-1.08)	0.882
Previous Aids event	1.28 (1.18-1.40)	<0.001
Residency area		
North	1.00	
Centre	1.23 (1.13-1.34)	<0.001
South	1.17 (1.01-1.35)	0.037
missing data	1.88 (1.74-2.03)	<0.001
Pre treatment CD4		
<=200	1.00	
201-350	0.70 (0.65-0.75)	<0.001
351-500	0.54 (0.50-0.59)	<0.001
500-max	0.36 (0.33-0.39)	<0.001
missing data	0.80 (0.67-0.96)	0.017
Pre treatment HIV RNA		
<4	1.00	
4-4.7	1.34 (1.23-1.45)	<0.001
4.8-5.2	1.66 (1.53-1.80)	<0.001
>5.2	2.06 (1.89-2.24)	<0.001
missing data	1.80 (1.53-2.13)	<0.001
Smokers		
no	1.00	
yes	0.93 (0.88-0.98)	0.008
missing data	0.81	<0.001
Pregnancy status		
not pregnant	1.00	
pregnant	5.33 (3.58-7.94)	<0.001
missing data	1.19 (1.02-1.38)	0.027
Calendar yr of cART start		
2002-2006	1.00	
2007-2011	1.21 (1.11-1.31)	<0.001
2012-2016	1.07 (0.98-1.17)	0.145

Saracino A. – Icona 2017

Results (2): ART response

Multivariable model of factors associated with virological response (HIV RNA <50)

✓ 5792 patients starting ART
with at least one year of follow-up



HR (95% CI)	p-value
0.97 (0.88-1.06)	0.468
0.97 (0.94-1.00)	0.085
1.00	
0.82 (0.74-0.91)	0.000
1.07 (0.99-1.14)	0.082
1.09 (0.97-1.22)	0.153
1.00	
1.11 (0.96-1.28)	0.150
1.17 (1.02-1.36)	0.030
1.22 (1.04-1.43)	0.017
1.10 (0.95-1.27)	0.223
1.00	
0.86 (0.78-0.95)	0.003
0.96 (0.89-1.04)	0.321
0.82 (0.67-1.00)	0.049
0.91 (0.78-1.07)	0.269
1.05 (0.89-1.24)	0.549
0.87 (0.73-1.05)	0.140
0.90 (0.75-1.07)	0.230
0.95 (0.87-1.05)	0.340
0.97 (0.88-1.08)	0.603
1.00	
1.08 (0.99-1.19)	0.084
0.79 (0.67-0.94)	0.006
0.99 (0.91-1.08)	0.860
1.00	
1.17 (1.08-1.27)	0.000
1.21 (1.11-1.33)	0.000
1.18 (1.07-1.31)	0.001
1.13 (0.92-1.39)	0.237
1.00	
0.92 (0.84-1.00)	0.063
0.75 (0.69-0.82)	0.000
0.59 (0.54-0.65)	0.000
0.78 (0.64-0.95)	0.013
1.00	
0.95 (0.90-1.01)	0.101
0.97 (0.86-1.09)	0.589
1.00	
0.94 (0.58-1.51)	0.797
1.08 (0.9-1.29)	0.374
1.00	
1.10 (1.01-1.20)	0.029
1.25 (1.13-1.38)	0.000

Saracino A. – Icona 2017

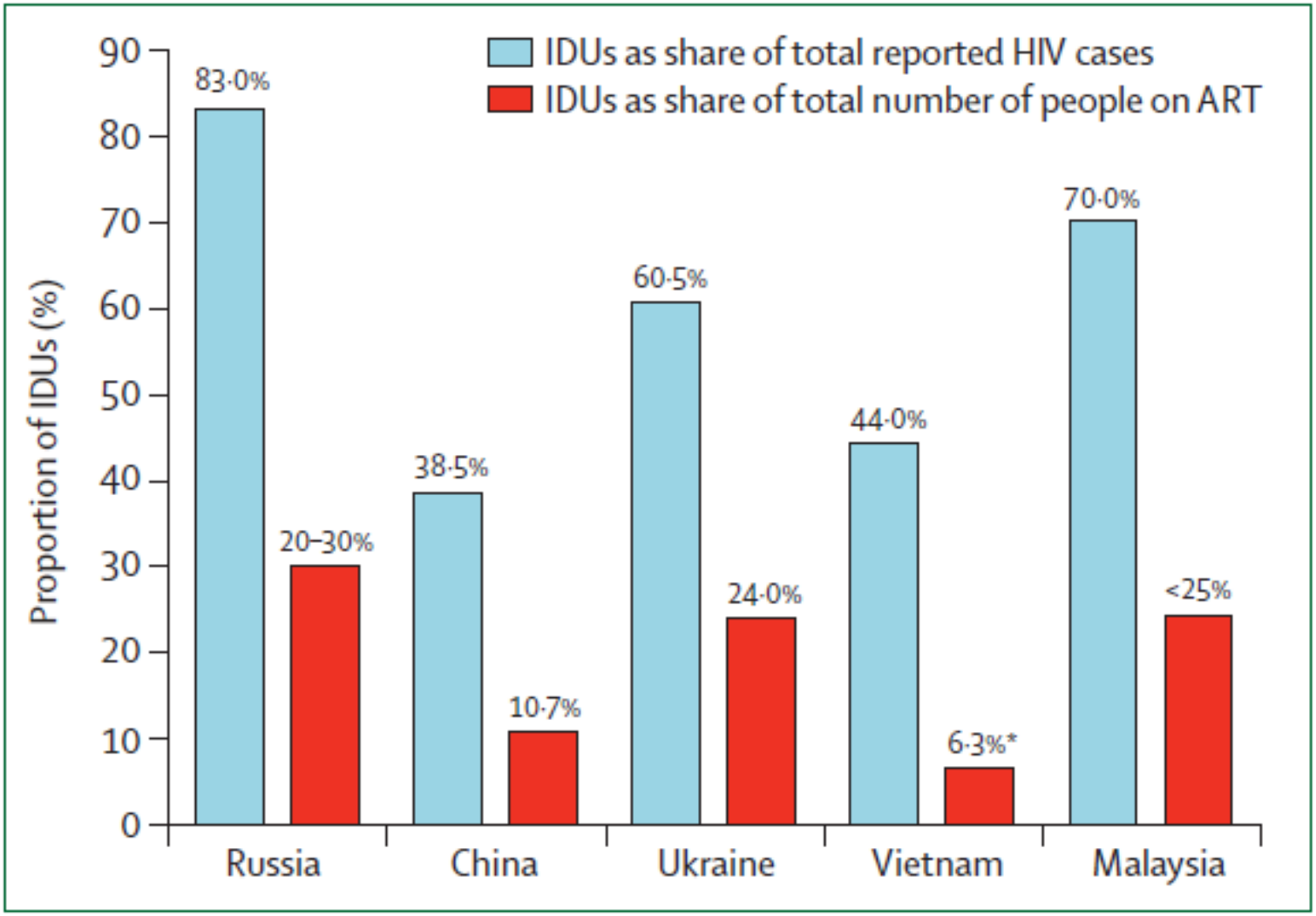
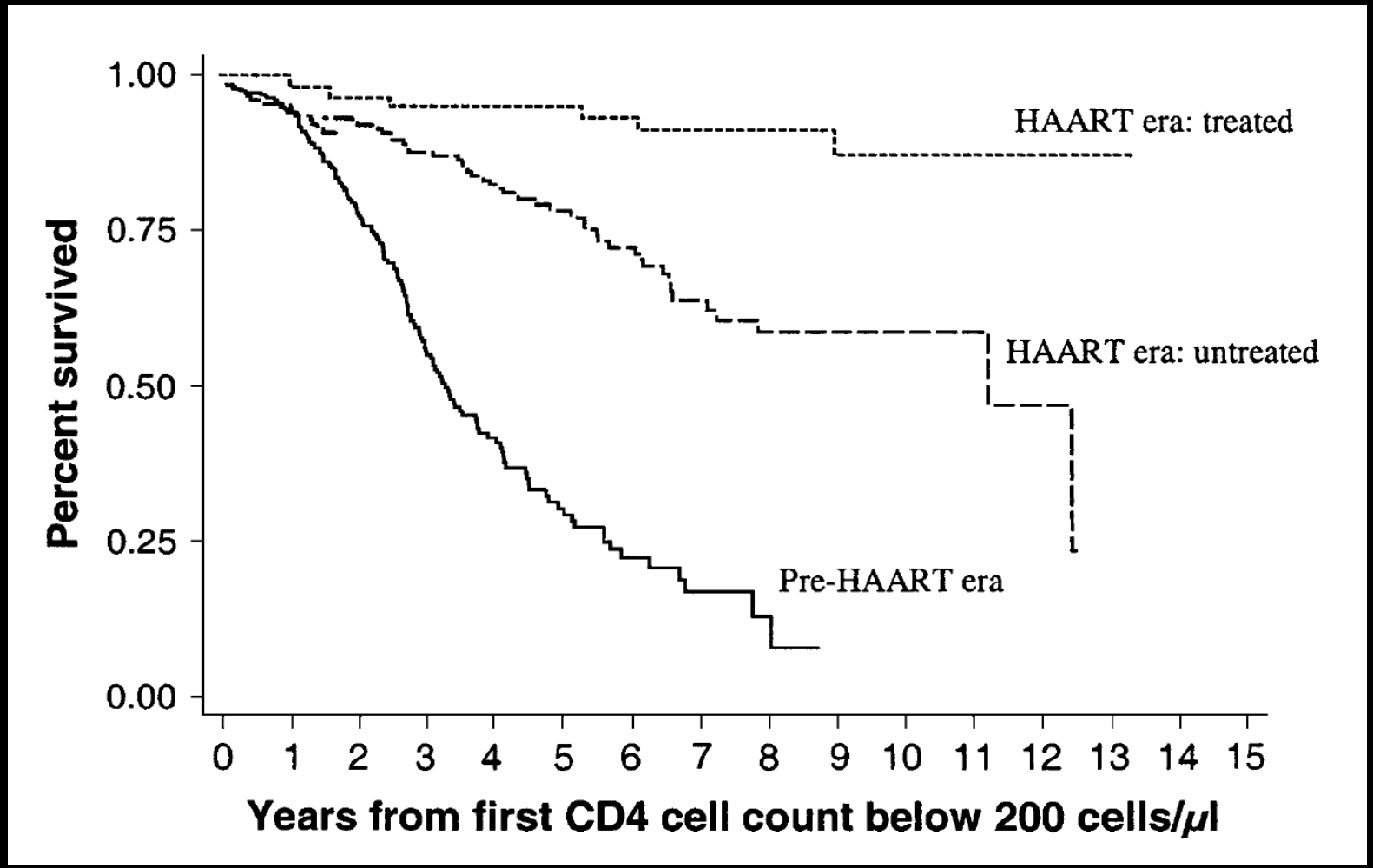


Figure 1: **IDUs as share of total HIV cases and of patients receiving ART, 2008**
Data sources: number of IDUs infected with HIV,[60] total HIV cases;[68] IDUs on ART in Russia,[69] China,[14] Ukraine,[70] Vietnam,[12,68] and Malaysia.[65] IDU=injecting drug user. ART=antiretroviral therapy. *Data are for 2009.

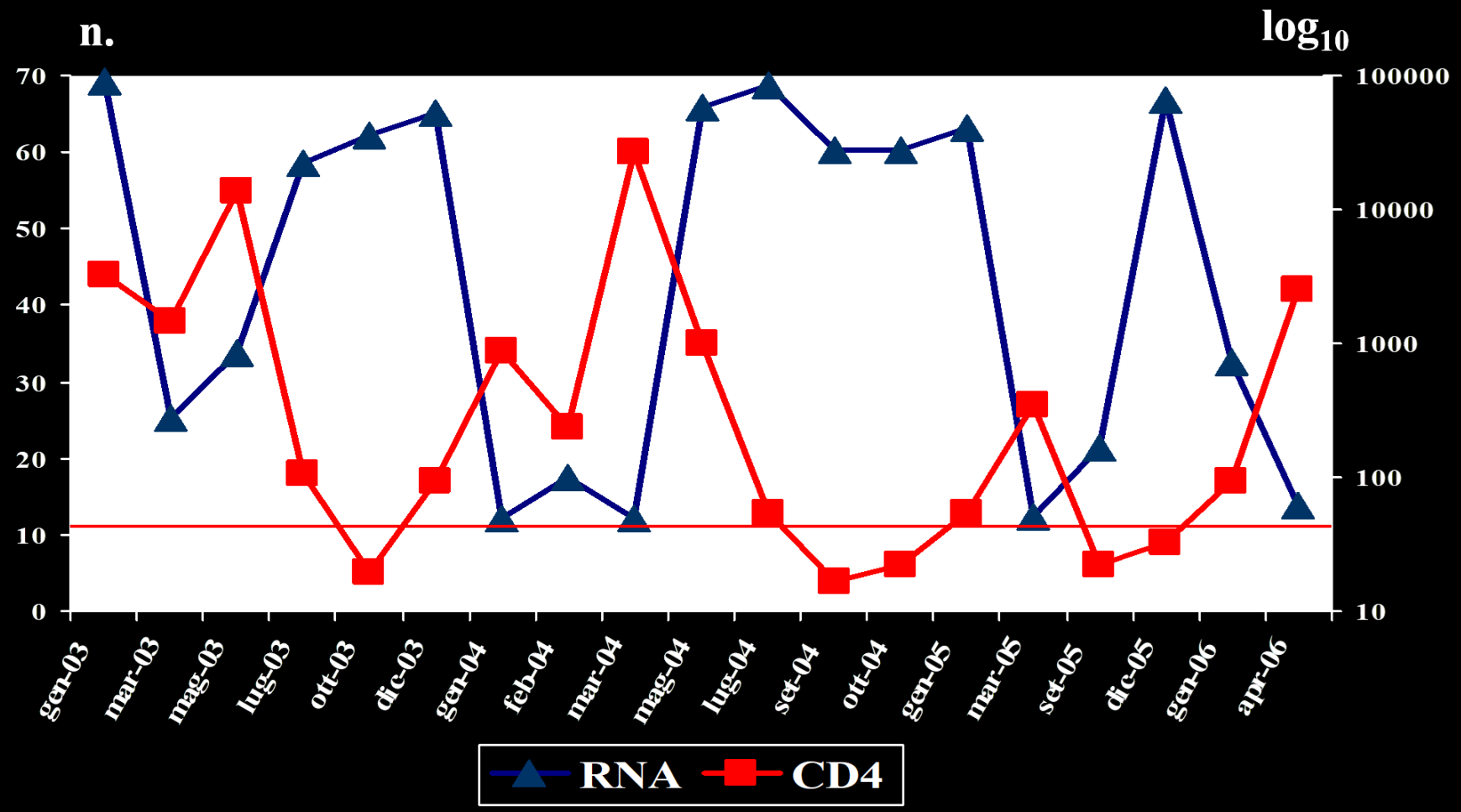
Wolfe,
Lancet 2010

Survival in HIV-infected drug users on HAART



Vlahov, Am J Epidemiol 2005

Case–report: CD4+ and HIV-RNA overtime in an active IDU patient with low CD4+ count



Associazione con non-aderenza

	Crude OR	P	Adjusted OR	P
Immigrato da paese a basso livello di risorse	1.09 (0.76-1.57)	0.646	1.22 (0.81-1.84)	0.331
Maschio	1.23 (0.90-1.67)	0.188	1.24 (0.89-1.72)	0.202
IVDU	**1.70 (1.26-2.29)**	**<0.001**	**1.59 (1.11-2.26)**	**0.011**
Età	0.83 (0.70-0.98)	0.026	0.86 (0.71-1.04)	0.114
Classe 3° farmaco schema in corso				
-nnrti	1.00		1.00	
-pi/r	1.36 (0.99-1.86)	0.055	1.25 (0.90-1.74)	0.194
-pi	1.13 (0.55-2.34)	0.740	1.11 (0.51-2.42)	0.783
-solo nrti	1.48 (0.75-2.95)	0.260	1.39 (0.68-2.82)	0.364
-nnrti+(pi o pi/r)	0.60 (0.15-2.46)	0.479	0.65 (0.14-2.92)	0.573
-almeno una nuova classe (t20 o mvc o rgv)	1.20 (0.38-3.83)	0.756	0.66 (0.18-2.43)	0.530
Anni tra 1° positività e test aderenza, mediana	**1.03 (1.01-1.05)**	**0.012**	1.01 (0.99-1.04)	0.270
CD4 al test (per 100)	0.98 (0.94-1.02)	0.379	1.00 (0.96-1.05)	0.824
log HIV-RNA al test	**1.72 (1.32-2.24)**	**<0.001**	**1.74 (1.30-2.32)**	**<0.001**

Zaccarelli, Personal Data

Associazione tra non-aderenza e uso attivo di droga autoriportato

Variabile	OR	95% CI	*p* value
Non-aderenza nell'ultima settimana	0.84	0.16-4.41	.83
Non aderenza negli ultimi 3 giorni	2.64	0.47-14.90	.27
Non accordo con le assunzioni di cibo	1.86	0.58-5.98	.30
Interruzioni spontanee >1 giorno	0.36	0.07-1.77	.21
Mancanza di rifornimento farmaci	6.23	2.03-19.09	.001

Aggiustato per trattamento con metadone

Multivariate association between Methadone treatment and non-adherence

Variabili	OR	95% CI	*p* value
Non-aderenza nell'ultima settimana	2.69	0.70-10.32	.15
Non aderenza negli ultimi 3 giorni	0.95	0.22-4.08	.94
Non accordo con le assunzioni di cibo	1.46	0.50-4.29	.49
Interruzioni spontanee >1 giorno	1.67	0.45.6.22	.44
Mancanza di rifornimento farmaci	1.40	0.44-4.44	.57

Adjusted by self-reported drug use

Zaccarelli, Adicona

Adherence to Antiretroviral Therapy in NY Drug Users

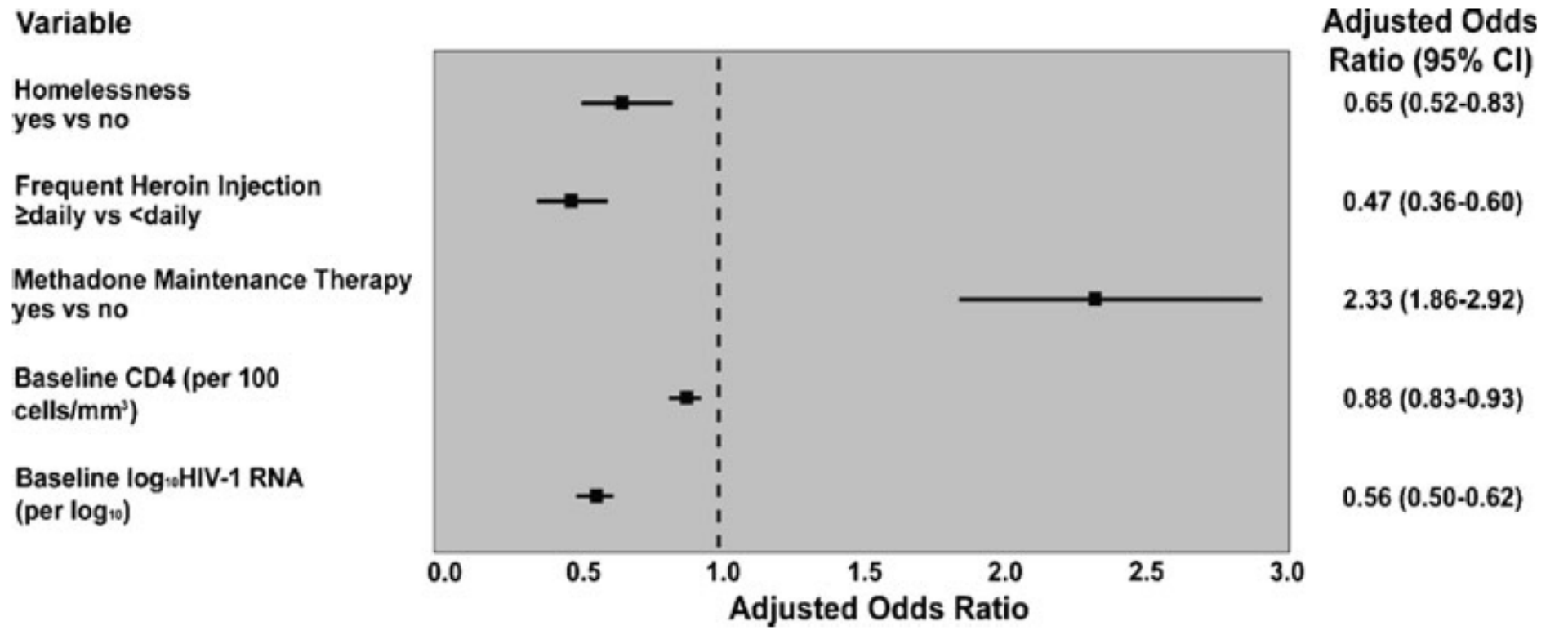


FIGURE 1. Multivariable logistic regression model using GEE of factors associated with 95% antiretroviral therapy adherence.

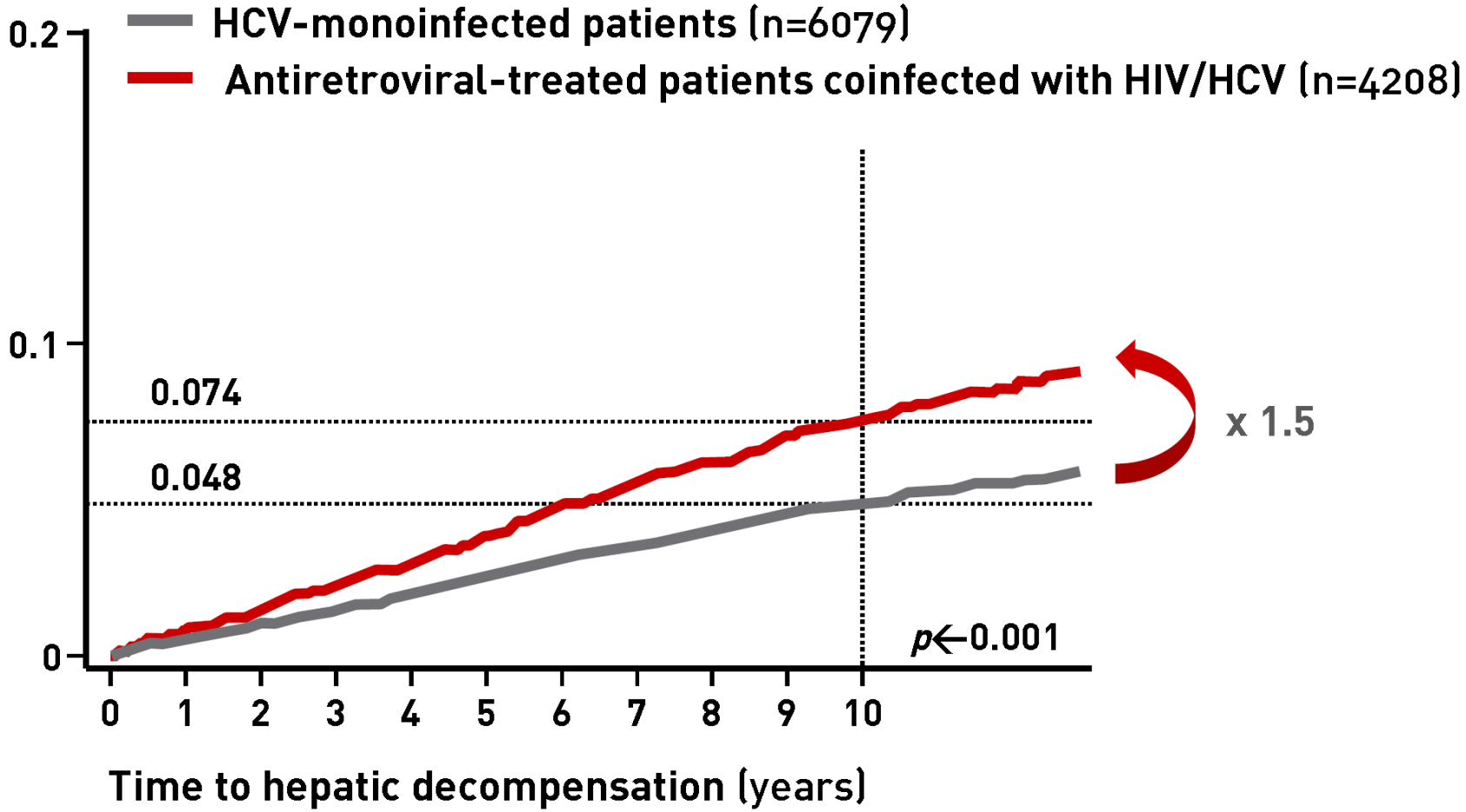
Multivariate analysis: factors associated with antiretroviral adherence in men and women (NY Bronx)

Factor	Beta	(95% CI)	*p* value
Long-term housing	16	(5.3 to 26.7)	.004
HIV support group	25.2	(12.3 to 38.2)	<.0005
Active crack or cocaine use	−18.3	(−31.2 to −5.4)	.006
Significant medication side effects	−22.5	(−34.2 to −10.9)	<.0005
Gender × problem alcohol use	−23.9	(−47.3 to −0.5)	.046
Problem alcohol use	0.50	(7.8 to 0.01)	.95
Gender (M = 0, F = 1)	−1.47	(6.45 to −0.023)	.82
Depression	4.05	(5.82 to 0.06)	.49

Berg, J Gen Int Med 2004

Epatite C e TD

HCV disease progression remains faster in coinfected patients, despite effective ART

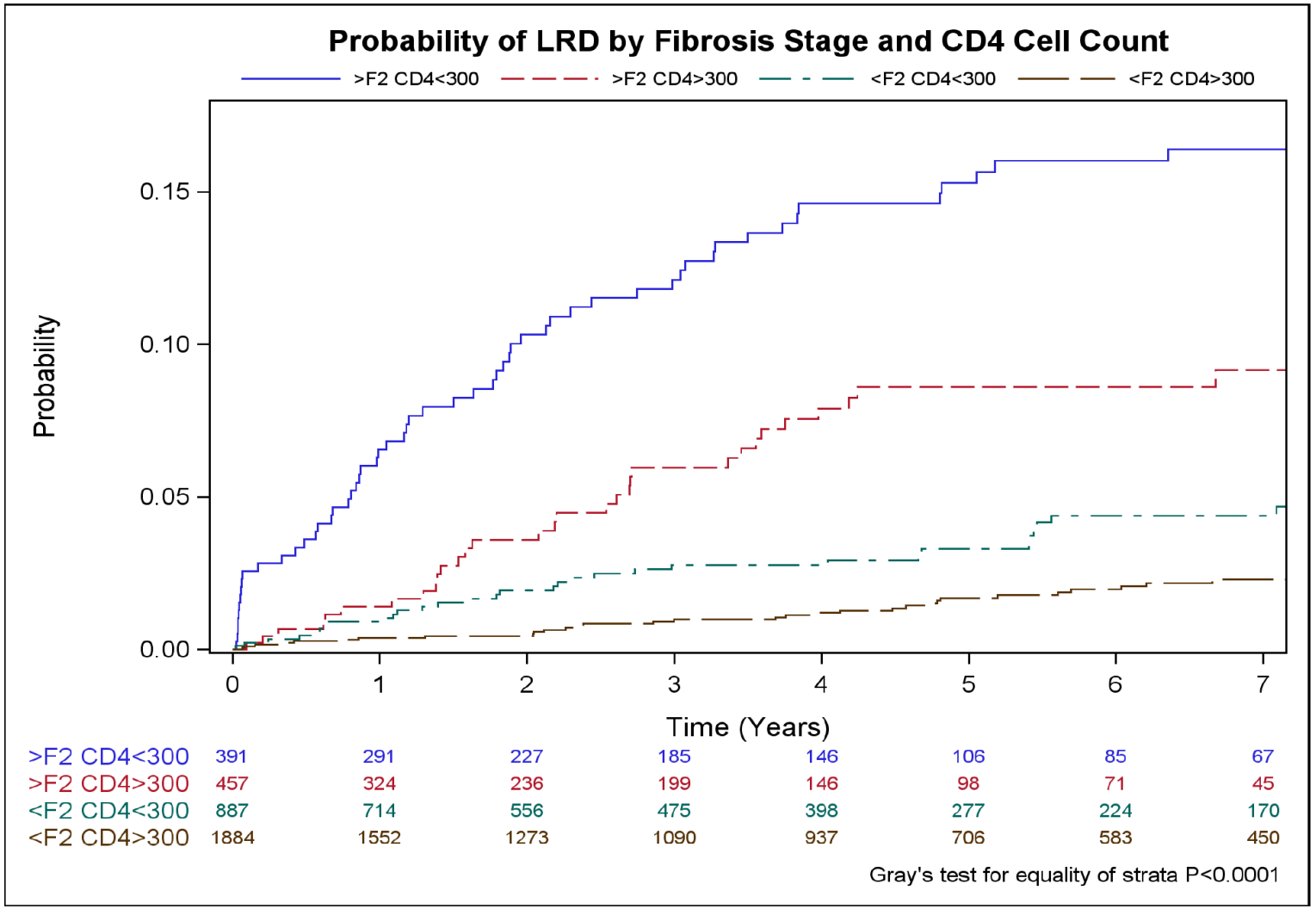


ART, antiretroviral therapy

Adapted from: Lo Re 3rd V, *et al. Ann Intern Med* 2014;160:369–79.

Cumulative incidence of LRD by fibrosis staging and CD4 cell count

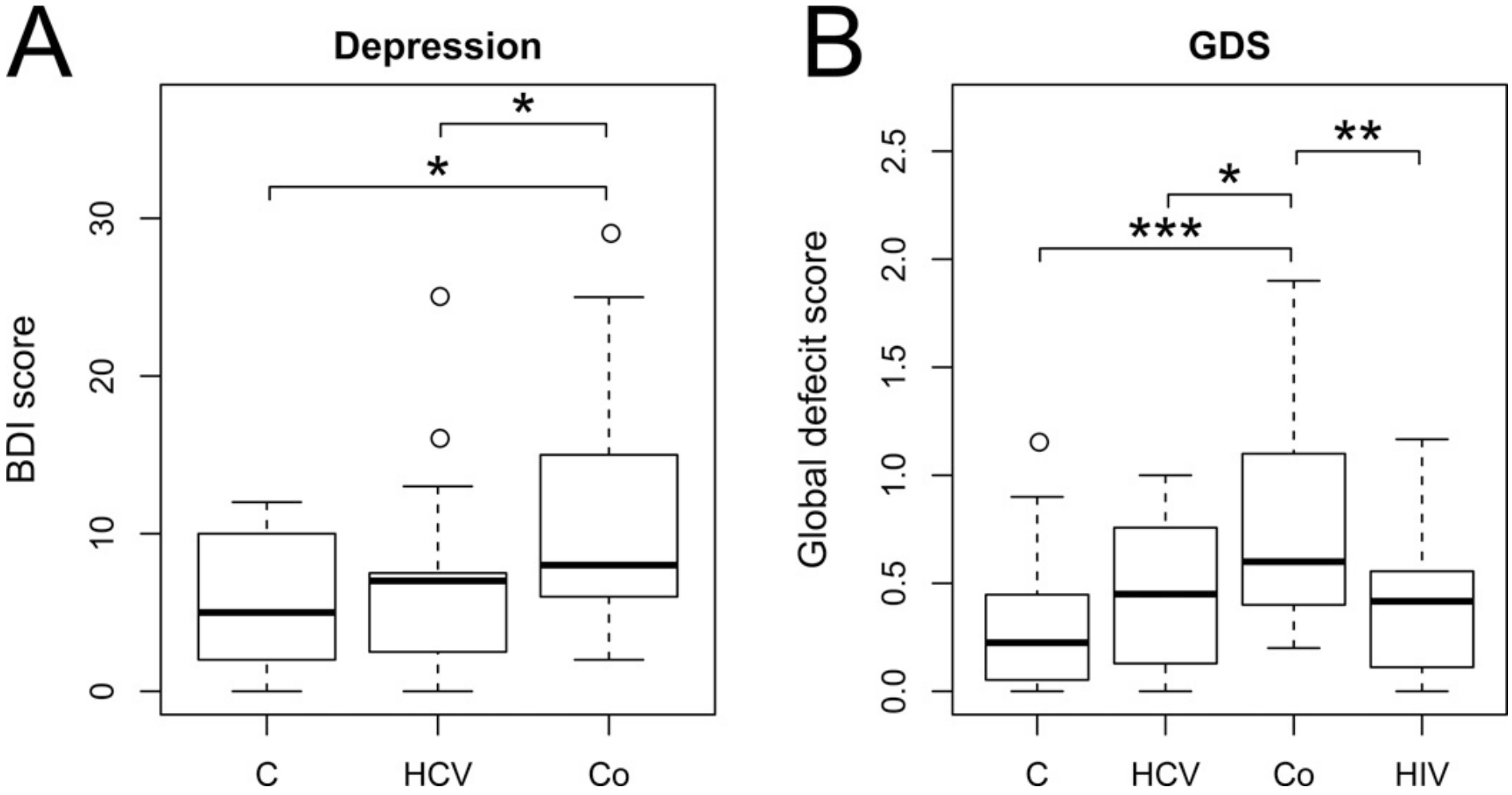
145 LRD among 3941 HIV/HCV pts from EuroSIDA



Grint et al CROI 2014

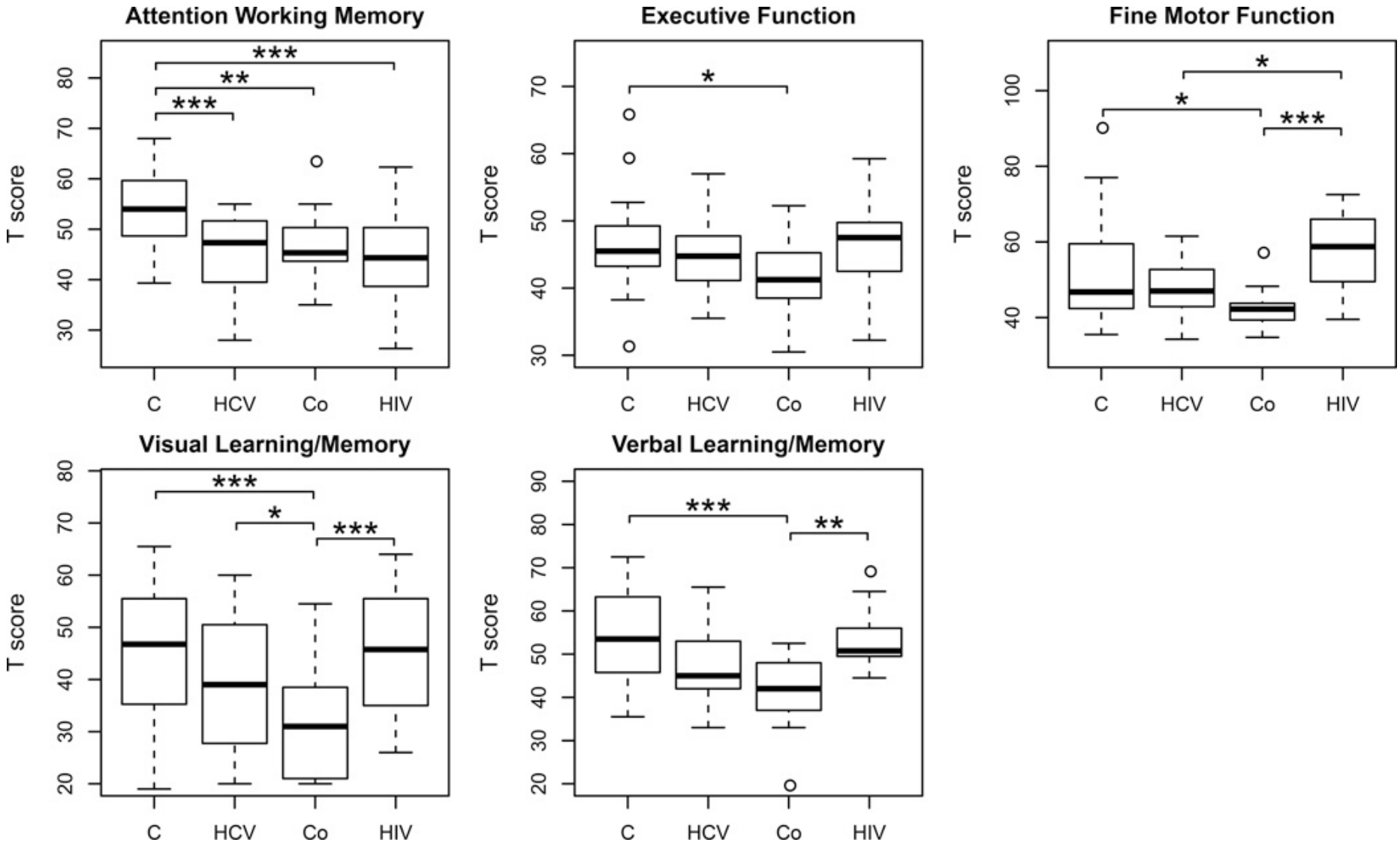
HIV/HCV e Deficit Cognitivo

- Accelerazione della progressione
- Ansia/depressione
- Effetto di farmaci (IFN)
- Crioglobuline/Ammonio
- Effetto Sinergico sul SNC di HIV/HCV
- Pazienti HCV/pazienti TD (effetto di droghe, problematiche psichiatriche, disadattamento sociale)



Group comparisons of depression and global deficit score. A) Comparisons of BDI scores for controls HCV and HIV/HCV infections. Controls were recruited in the HCV cohort. B) Comparisons of controls, HCV monoinfection, HIV/HCV coinfection and HIV monoinfection of GDS scores. Controls were used from both HCV and HIV cohorts. *p<0.05, ** p<0.01, ***p<0.001 using MANOVA with education and IQ adjusted. BDI=Beck depression inventory–II score. GDS=global deficit score. C=controls, HCV=HCV monoinfection, Co=HIV/HCV coinfection.

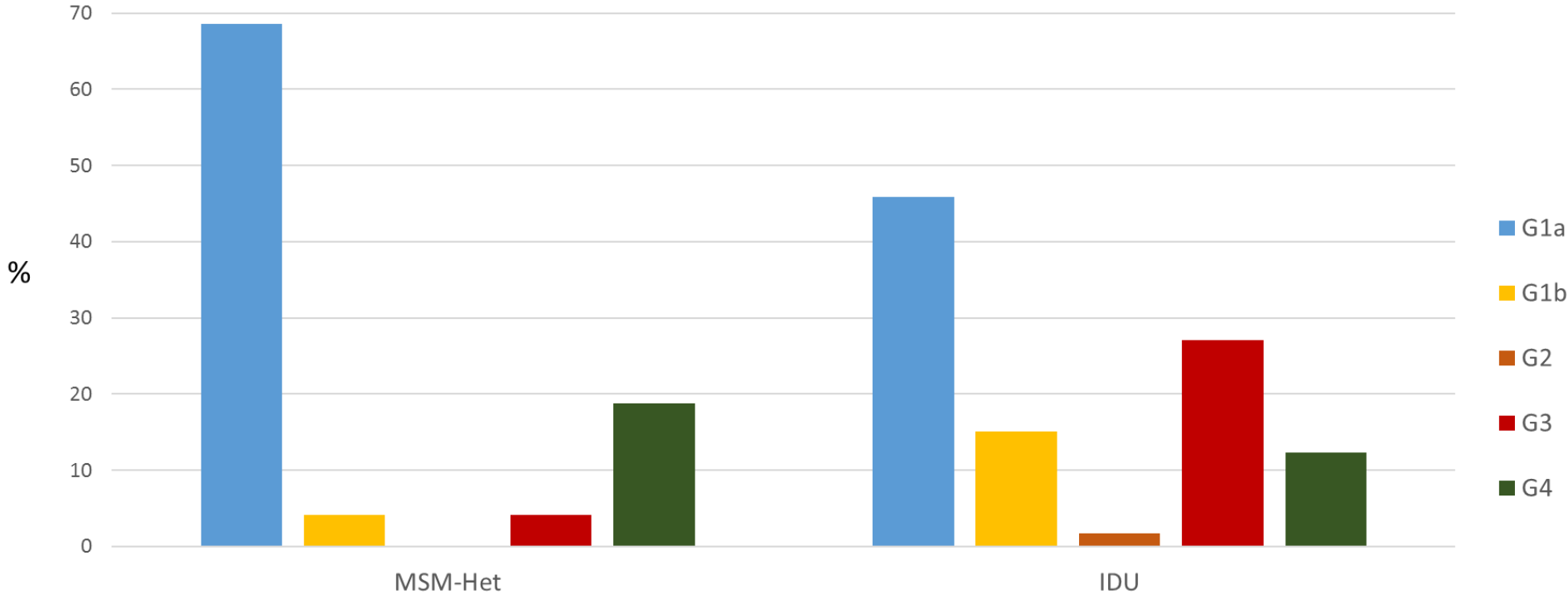
Sun, JAIDS 2017



Group comparisons of significant neuropsychological domains. MANOVA analyses with education and IQ adjusted were used to compare group means. * p<0.05, ** p<0.01, *** p<0.001. C=controls, HCV=HCV monoinfection, Co=HIV/HCV coinfection, HIV=HIV monoinfection.

Sun, JAIDS 2017

Distribuzione genotipo HCV (Coinfetti Spallanzani)



Mastrorosa, ICAR 2017

Table 4B. Drug-drug interactions between HCV DAAs and illicit recreational drugs.

	SOF	SOF/ LDV	SOF/ VEL	3D	GZR/ EBR	DCV	SIM
Amphetamine	◆	◆	◆	■	◆	◆	◆
Cannabis	◆	◆	◆	■	◆	◆	■
Cocaine	◆	◆	◆	■	◆	◆	■
Diamorphine	◆	◆	◆	■	◆	◆	◆
Diazepam	◆	◆	◆	■	◆	◆	■
Gamma-hydroxybutyrate	◆	◆	◆	■	◆	◆	■
Ketamine	◆	◆	◆	■	◆	◆	■
MDMA (ecstasy)	◆	◆	◆	■	◆	◆	◆
Methamphetamine	◆	◆	◆	■	◆	◆	◆
Phencyclidine (PCP)	◆	◆	◆	■	◆	◆	■
Temazepam	◆	◆	◆	◆	◆	◆	◆

SOF, sofosbuvir; SOF/LDV, sofosbuvir plus ledipasvir; SOF/VEL, sofosbuvir plus velpatasvir; 3D, ritonavir-boosted paritaprevir, plus ombitasvir and dasabuvir; GZR/EBR, grazoprevir plus elbasvir; DCV, daclatasvir; SIM, simeprevir.

Colour legend

◆ No clinically significant interaction expected.

■ Potential interaction which may require a dosage adjustment, altered timing of administration or additional monitoring.

● These drugs should not be co-administered.

EASL 2016

DAA in clinical practice…

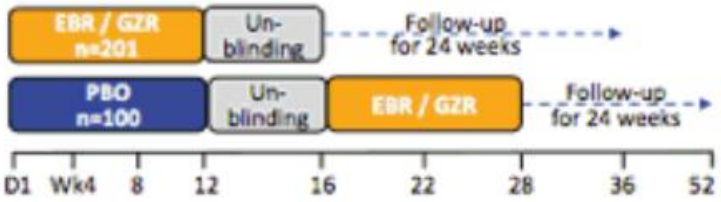
Figure 1. Green figures represent the number of Canadian Coinfection Cohort participants who would be eligible to be screened in NCT01479868 (trial evaluating simeprevir); PHOTON-1: NCT01667731 (trial evaluating sofosbuvir); TURQUOISE-I: NCT01939197 (trial evaluating ombitasvir, paritaprevir/ritonavir/dasabuvir [3D]); ION-4: NCT02073656 (trial evaluating ledipasvir/sofosbuvir); and ALLY-2: NCT02032888 (trial evaluating daclatasvir/sofosbuvir). Gray figures represent participants whose only exclusion was specific antiretroviral (ARV) therapies. Red figures represent participants not eligible regardless of ARV restriction.

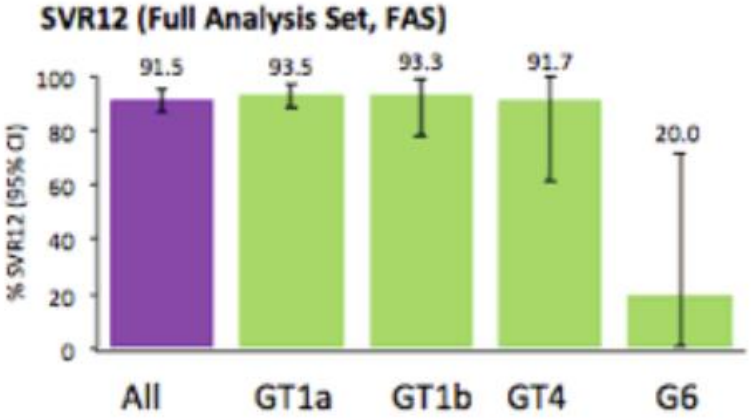
Reference	Patients	SVR12	Predictors of failure
Piroth L. et al. J. Hepatology 2017	323 HIV/HCV co-infected	93.5%	/
Bhattacharya D. et al. Clin. Infect. Dis. 2017	905 HIV/HCV co-infected	90.9%	/
Milazzo L. et al. HIV Medicine 2017	51 HCV mono-infected	96%	/
	58 HIV/HCV co-infected	91%	
Montes M.L. et al. AIDS 2017	1152 HCV mono-infected	96.7%	Cirrhosis Sofosbuvir + simeprevir +/- ribavirin
	482 HIV/HCV co-infected	94.2%	

1.Saeed S, *et al*. Canadian Co-Infection Cohort Study. *Clin Infect Dis* 2016. 2. Piroth L, *et al.* French ANRS CO13 HEPAVIH cohort. *J Hepatol* 2017.
3. Bhattacharya D, *et al. Clin Infect Dis* 2017. 4. Milazzo L., *et al. HIV Med* 2017. 5. Montes ML, *et al.* The HULP-HUGM Study Group Investigators. *AIDS* 2017.

C-EDGE CO-STAR: Efficacy of GZR + EBR in PWID receiving opioid agonist therapy (OAT)

- Phase 3, double-blind RCT in pts on OAT for >3 months
  - 20% with cirrhosis
  - 7% HIV coinfected
  - 79% had positive drug toxicology during follow up





Highly efficacious HCV treatment will only be effective if HCV infected patients are treated

Oluwaseun Falade-Nwulia, CROI 2016

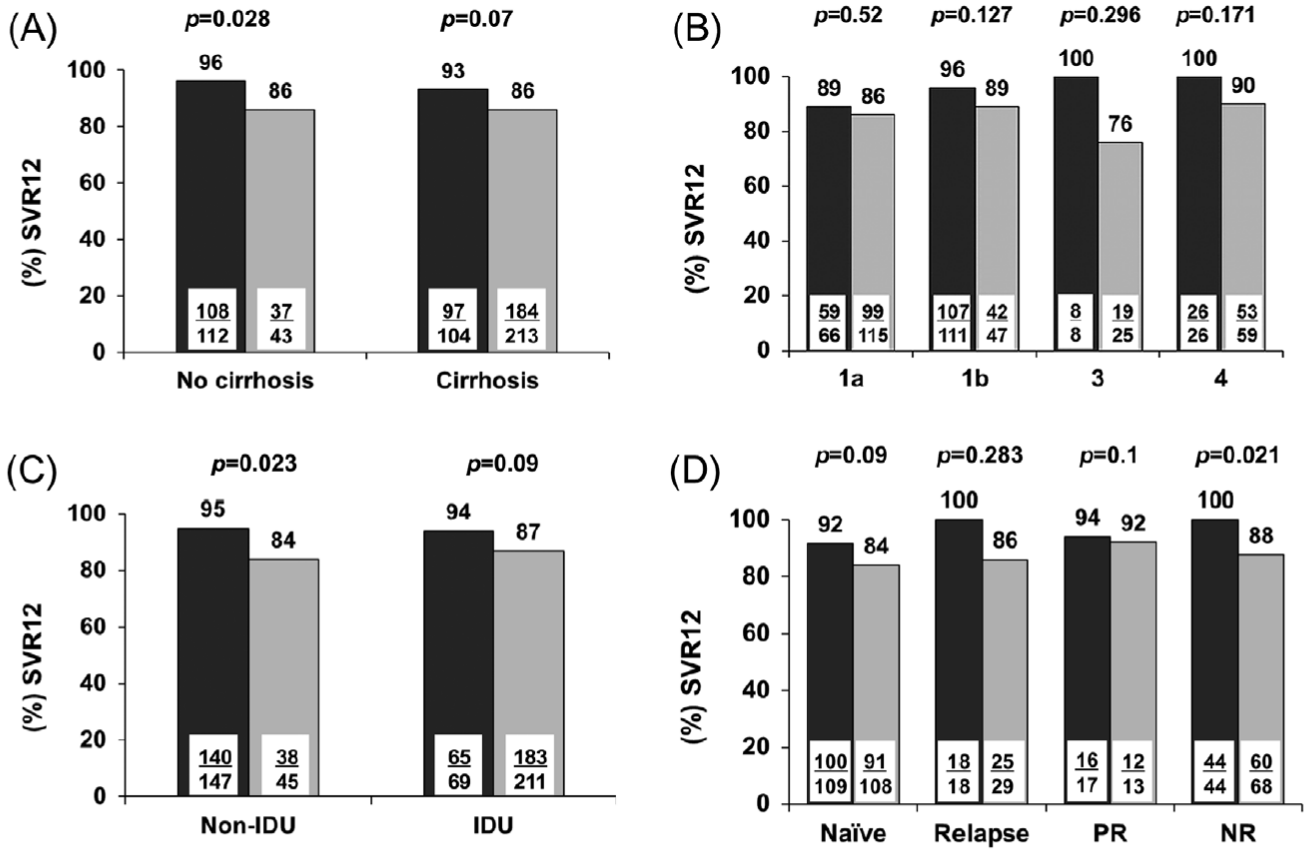


Figure 2 Rates of sustained virologic response 12 weeks after scheduled end-of-therapy (SVR12) to interferon-free, all oral treatment regimens including at least two direct-acting antivirals with or without ribavirin according to (A) baseline cirrhosis, (B) HCV genotype, (C) prior injecting drug use (IDU) and (D) response to previous therapy with pegylated interferon plus ribavirin in an intention-to-treat approach. Dark bars: HCV-monoinfected patients; light bars: HIV/HCV-coinfected patients; SVR12: Sustained virologic response 12 weeks after scheduled end-of-therapy. PR: partial response; NR: null response

Neukan, HIV Clin Trials 2017

Fattori che possono influenzare il fallimento terapia co DAA nei pazienti con coinfezione HIV/HCV

Immunosoppressione

Interazioni farmacologiche

Tossicità epatica della terapia

Condizioni cliniche compromesse

Fattori legati allo stile di vita dei pazienti

- Uso di droghe o alcool
- Aderenza inadeguata
- Problemi psichiatrici

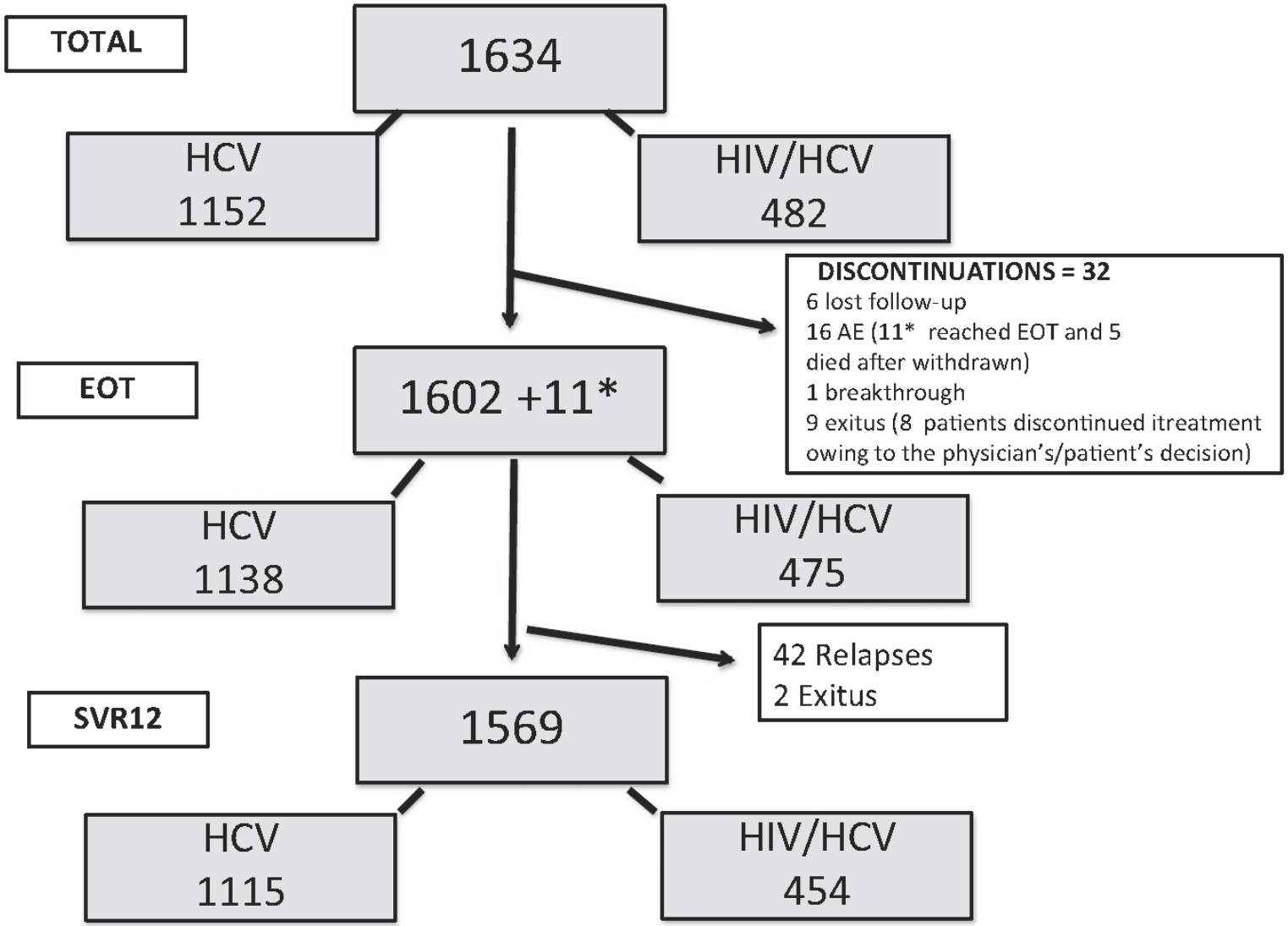


Fig. 1. Flow of patients through the study. AE, adverse events; EOT, end of treatment.

Montes, AIDS 2017

Problematiche riscontrate nell'esperienza di trattamento con DAA dei pazienti coinfetti

- Interruzioni spontanee durante il trattamento
- Assunzione non corretta dei farmaci durante il trattamento (es. doppia dose quotidiana)
- Fine terapia anticipato dal paziente
- Appuntamenti di prelievi o visite saltati
- Interruzione della ribavirina per effetti collaterali
- Decesso
- Errori di genotipo HCV
- Declino più lento della viremia di HCV e viremia rilevabile a fine terapia

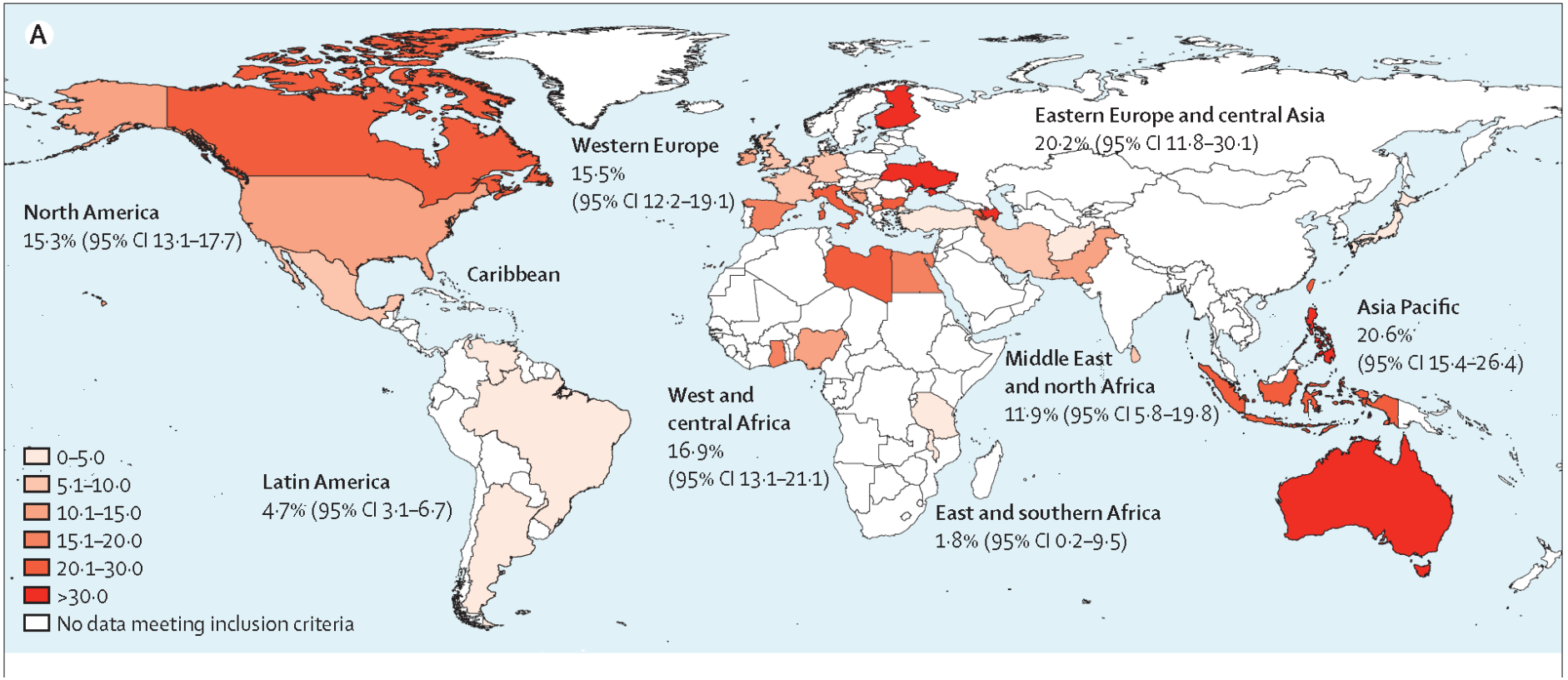
Il Problema del Carcere

	Prison population*	General population HIV prevalence (LE and UE)†	Pooled HIV prevalence in prison populations (95% CI)	Pooled HBV prevalence in prison populations (95% CI)‡	Pooled HCV prevalence in prison populations (95% CI)§	Pooled tuberculosis prevalence in prison populations (95% CI)¶
Eastern and southern Africa	588 000	4·7% (4·4–4·9)	15·6% (11·8–19·8)	5·7% (2·9–9·4)	1·8% (0·2–9·5)	5·3% (2·1–10·0)
Western and central Africa	201500	4·7% (4·4–4·9)	8·2% (6·2–10·5)	23·5% (19·8–27·5)	16·9% (13·1–21·1)	2·9% (2·4–3·6)
Middle East and north Africa	645 000	0·1% (<0·1–0·2)	1·3% (0·2–3·3)	3·3% (2·4–4·5)	11·9% (5·8–19·8)	..
Asia and Pacific	3 344 500	0·2% (0·2–0·2)	1·4% (0·9–1·9)	4·4% (1·4–9·0)	20·6% (15·4–26·4)	1·2% (0·7–1·7)
Eastern Europe and central Asia	1287 000	0·6% (0·6–0·8)	4·1% (1·4–8·0)	10·4% (1·9–24·6)	20·2% (11·8–30·1)	4·9% (1·8–9·3)
Western Europe	412 000	0·3% (0·3–0·5)	4·2% (2·7–6·1)	2·4% (1·6–3·3)	15·5% (12·2–19·1)	..
North America	2 255 000	0·3% (0·3–0·5)	1·3% (1·0–1·7)	1·4% (0·3–3·1)	15·3% (13·1–17·7)	..
Caribbean	109 000	1·1% (0·9–1·2)	3·3% (2·7–4·0)	..	..	..
Latin America	1 400 000	0·4% (0·4–0·6)	2·3% (1·5–3·4)	2·3% (0·1–8·3)	4·7% (3·1–6·7)	2·0% (1·3–2·7)

All pooled prevalence estimates include only biologically confirmed test results and exclude those that are self-reported measures. Data are from Dolan and colleagues.[1] LE=lower estimate. UE=upper estimate. HBV=hepatitis B virus. HCV=hepatitis C virus. *Prison population estimates have been rounded to the nearest 500 people. †Data are from UNAIDS Gap Report 2014;[2] HIV estimates for western and central Africa and eastern and southern Africa are reported under sub-Saharan Africa, and HIV estimates for western Europe and North America are reported jointly as western Europe and North America in the Gap Report. ‡HBV infection is determined via HBsAg testing. §HCV infection is determined by anti-HCV testing. ¶Active tuberculosis disease is determined by any of the following: tuberculin skin test, smear microscopy, culture, genetic testing, or chest radiograph with confirmatory diagnostics.

***Table 1*: Regional HIV, hepatitis B virus, hepatitis C virus, and tuberculosis infection in prisoners**

Kamarulzaman, Lancet 2016



Global and regional prevalence of hepatitis C in prison inmates, published between 2005 and 2015

Dolan, Lancet 2016

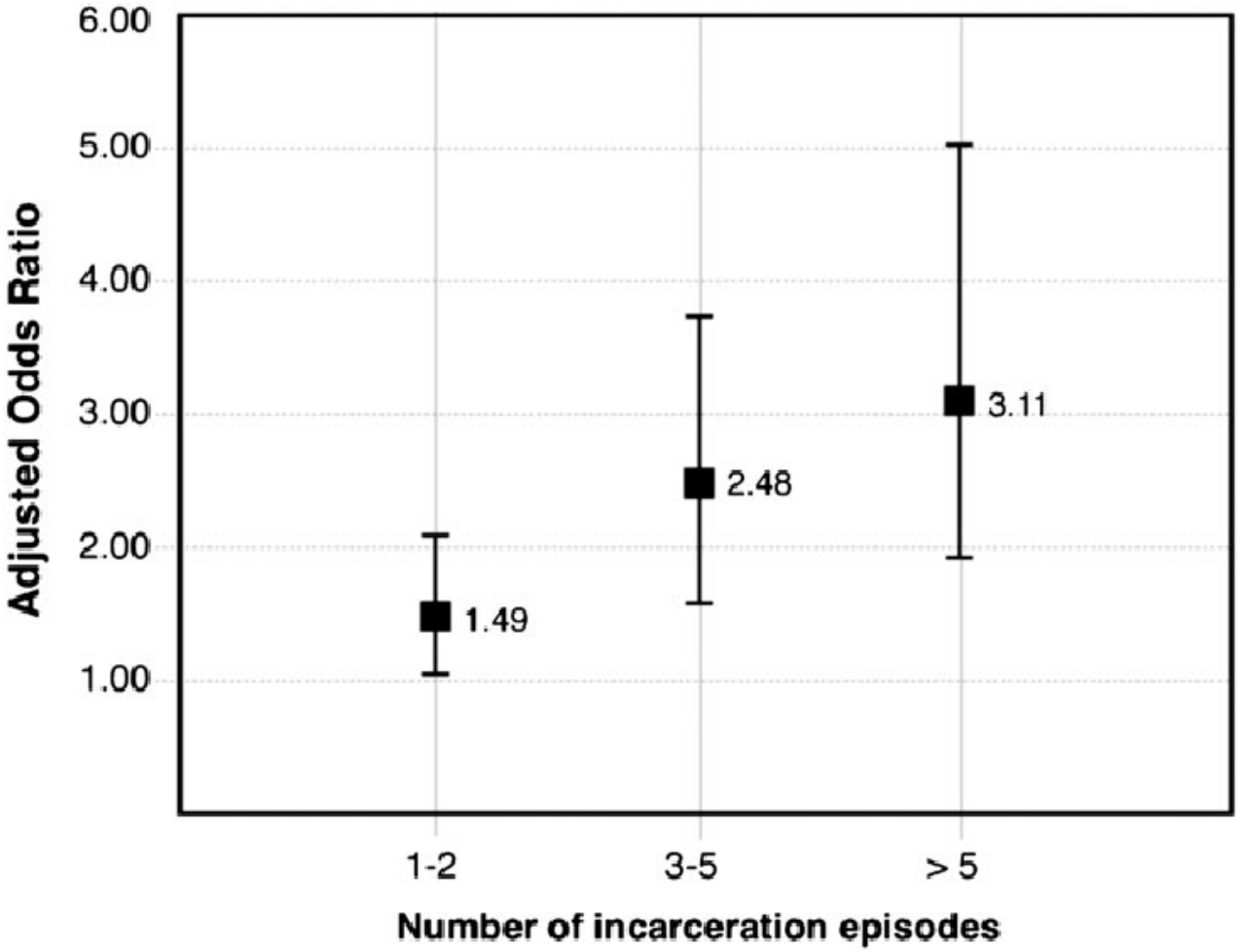
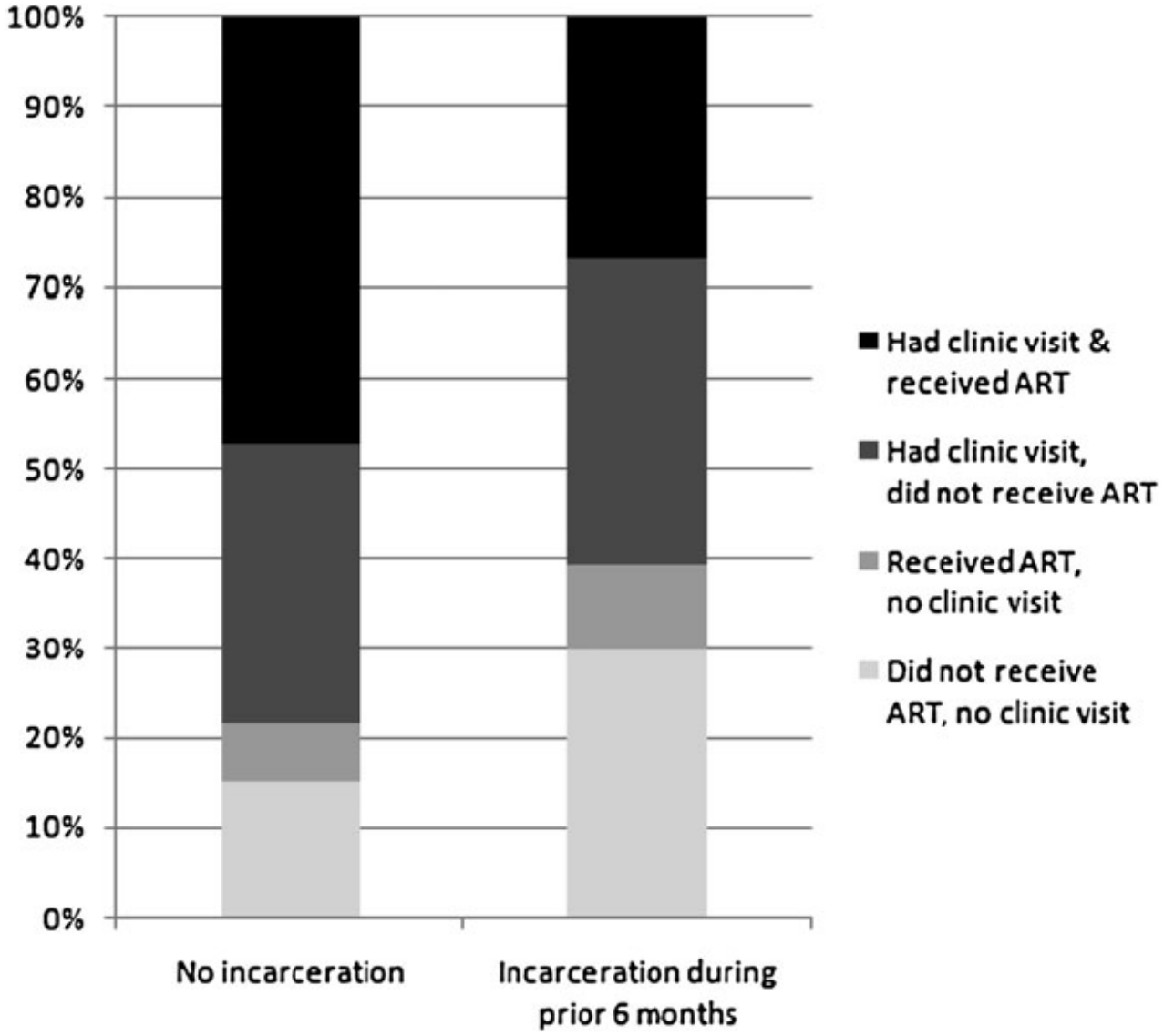


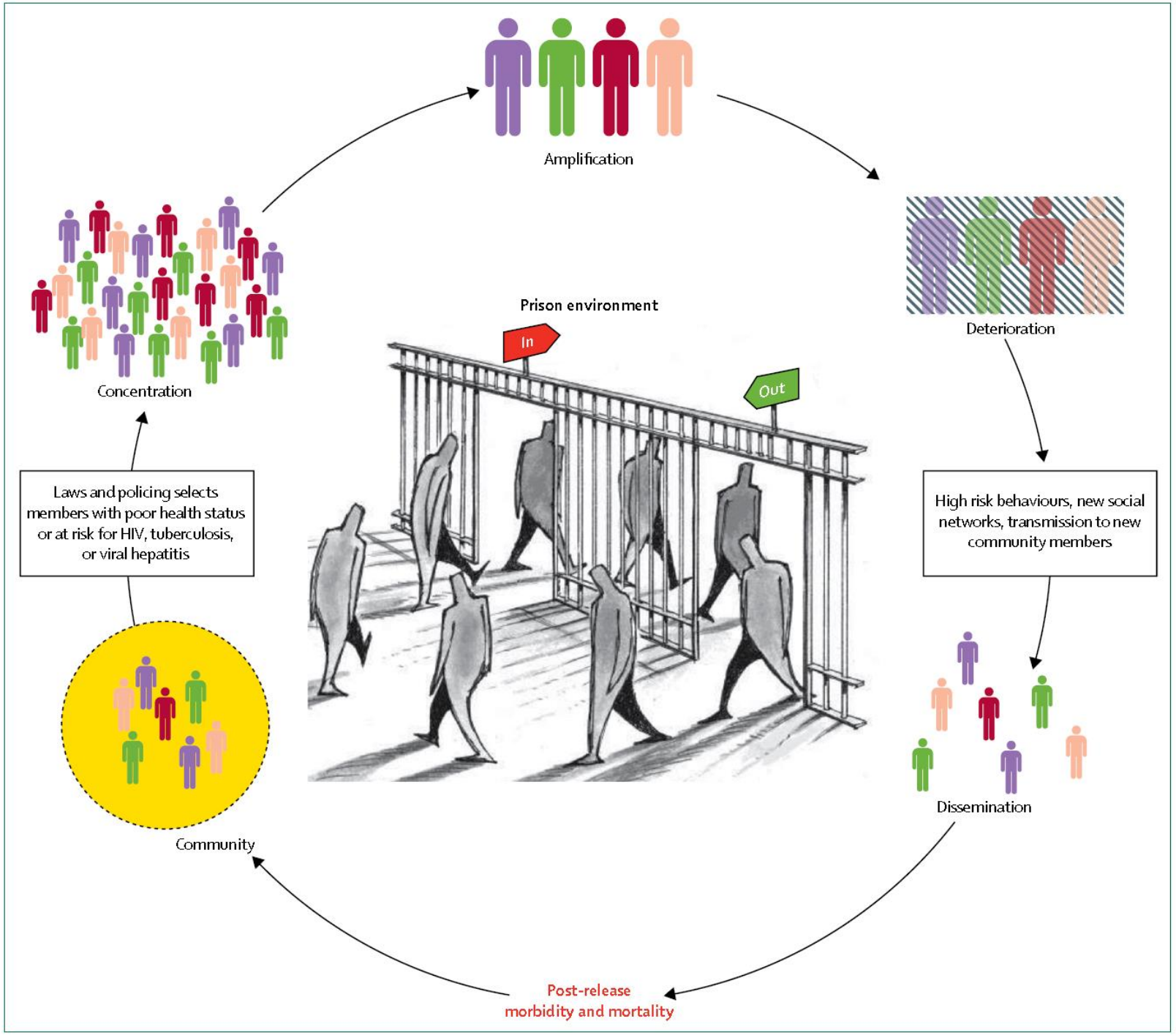
Figure 2. Adjusted odds ratios for nonadherence to ART by number of incarceration episodes among 490 ART-exposed IDUs in Vancouver, Canada. Multivariate model adjusted for sex, daily injection cocaine use, number of months since ART initiation, methadone maintenance therapy, and plasma HIV-1 RNA load.

Milloy (Vancouver), JID 2010

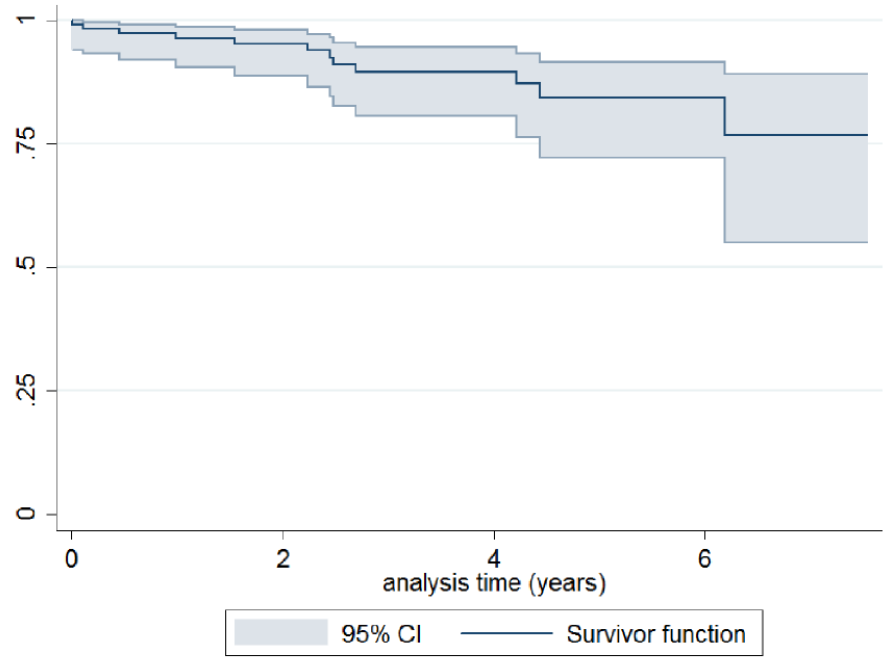


Westergaard, CID 2011

Figure 1. Recent antiretroviral therapy (ART) use and outpatient clinic attendance according to incarceration history for 437 injection drug users (IDUs) in ALIVE (2075 study visits).



Kamarulzaman, Lancet 2016



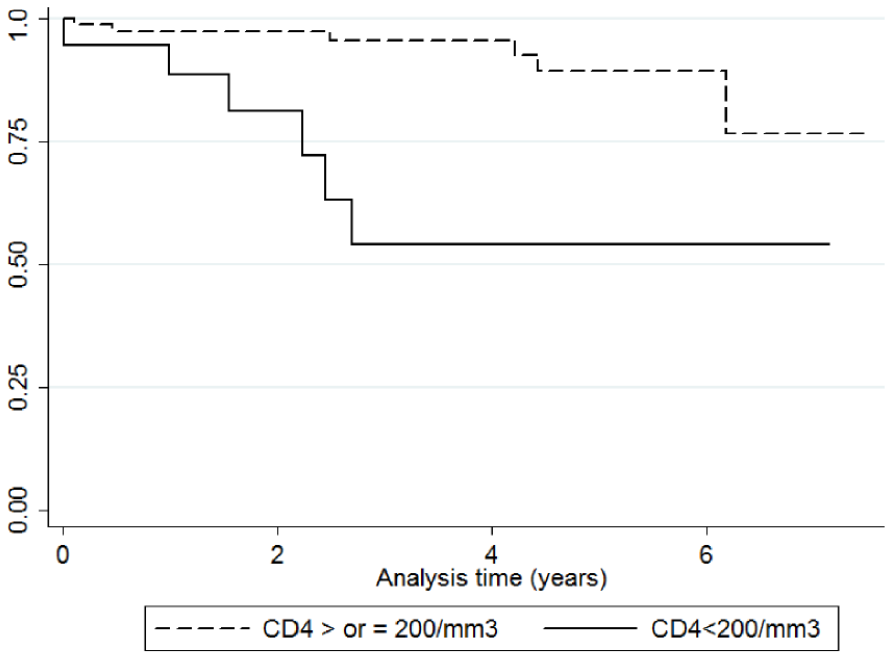


Fig 2. Mortality following release from the French Guiana CF (Kaplan-Meier survival estimate),

Post-release mortality rate was extraordinary high among men, with a **standardized mortality ratio at 14.8**, compared with the general French Guianese population.

As elsewhere, CD4 count and age were associated with the risk of death. Other variables, like housing status, may have a strong impact, but our small sample was not able to show it.

Medical care with ART is not sufficient to help HIV-positive former inmates to stay alive in the years following their release from correctional facilities.

Huber, PlosOne 2017

Grazie per l'attenzione….

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