

Complessità e gestione della co-morbilità infettivologica

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Disclosures

I have received funding for membership of Advisory Boards, for the preparation of educational materials, for research and educational grants, for membership of speaker panels and for support for travel to conferences from the following companies:

- **Gilead Sciences**
- **Bristol-Myers Squibb**
- **Janssen-Cilag**
- **Viiv Healthcare**
- **Abbott Pharmaceuticals**
- **Merck Sharp and Dohme**
- **Abbvie**
- **Angelini**
- **Boehringer Ingelheim**
- **Pfizer**

Infectious agents transmitted with blood

- HIV 1/2
- HTLV I/II
- Hepatitis B
- Hepatitis C
- Syphilis
- CMV
- HHV-8
- Parvovirus B19
- Malaria
- Chagas' disease
- Lyme disease
- vCJD
- West Nile Virus
- SARS
- Orthopoxviruses
- Chlamydia pneumoniae
- Bacteria Gram- and gram+
- Fungi
- Babesiosis

Integrated Prevention Services for HIV Infection, Viral Hepatitis, Sexually Transmitted Diseases, and Tuberculosis for Persons Who Use Drugs Illicitly: Summary Guidance from CDC and the U.S. Department of Health and Human Services



Continuing Education Examination available at <http://www.cdc.gov/mmwr/cme/conted.html>.



U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

Summary of recommended screening, counseling, and vaccination services for persons who use drugs illicitly

- ✓ **HIV: test (at least annually)**
- ✓ **HAV: vaccination is recommended**
- ✓ **HBV: vaccination is recommended**
- ✓ **HCV: test (at least annually)**
- ✓ **Tuberculosis: targeted testing programs**
- ✓ **Chlamydia: annual screening**
- ✓ **Gonococcal infections**
- ✓ **Syphilis**
- ✓ **Herpes simplex virus-2**
- ✓ **Human papillomavirus (HPV)**

Integrated Prevention Services for HIV Infection, Viral Hepatitis, Sexually Transmitted Diseases, and Tuberculosis for Persons Who Use Drugs Illicitly: Summary Guidance from CDC and the U.S. Department of Health and Human Services



Continuing Education Examination available at <http://www.cdc.gov/mmwr/cme/conted.html>.

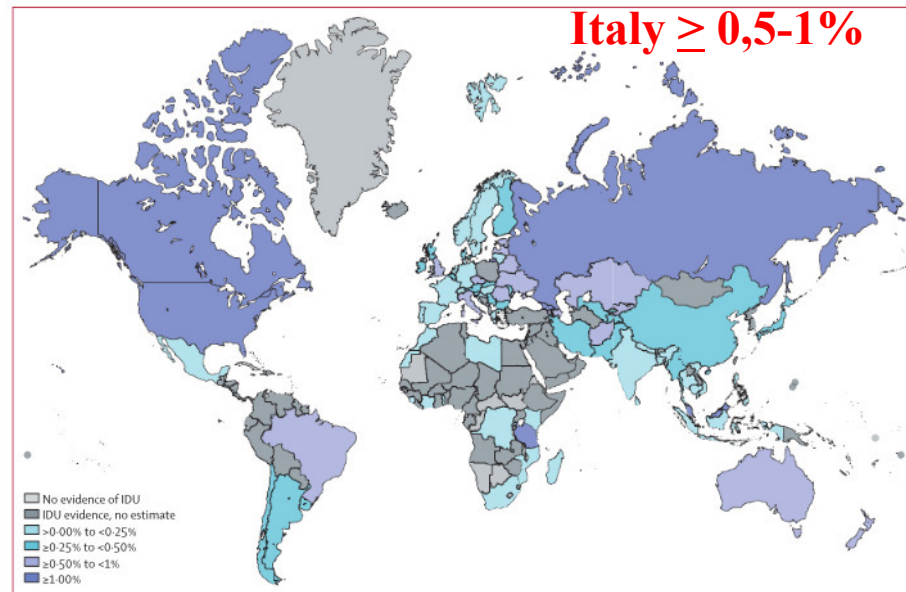


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- ✓ **Syphilis***
- ✓ **Herpes simplex virus-2**
- ✓ **Human papillomavirus (HPV)**

Estimated prevalence of injecting drug use by country



The global burden of TB

Estimated number of cases

**All forms of TB
(men and women)**

9.4 million
(range, 8.9–9.9 million)

HIV-associated TB

1.1 million (12%)
(range, 1.0–1.2 million)

**Multidrug-resistant
TB (MDR-TB)**

0.5 million

Estimated number of deaths

1.3 million*
(range, 1.2–1.5 million)

0.4 million
(range, 0.32–0.45 million)

~ 0.15million

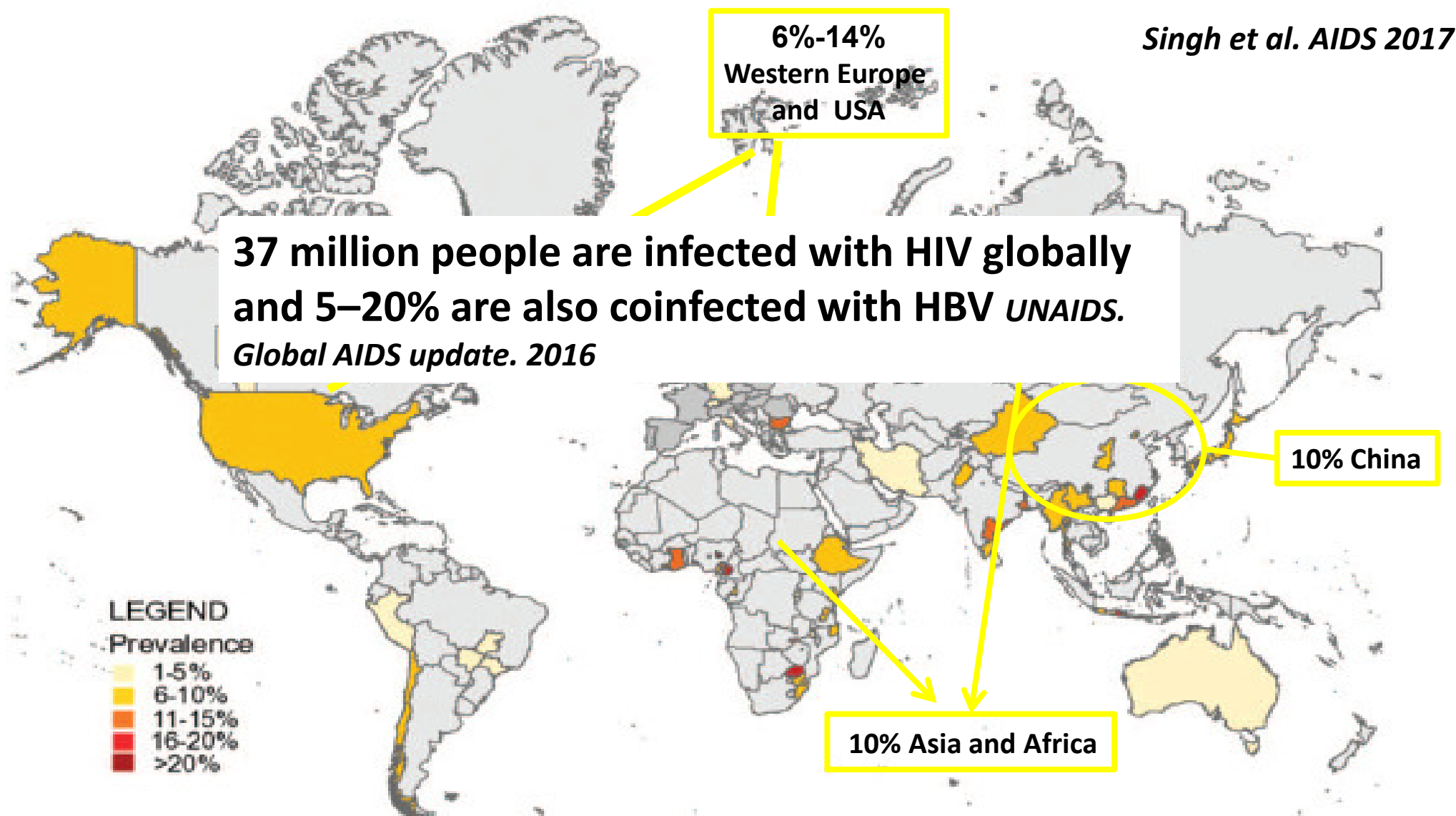
- Risk of TB in PWID: 20-40X
- Isoniazid prevents TB in PWID



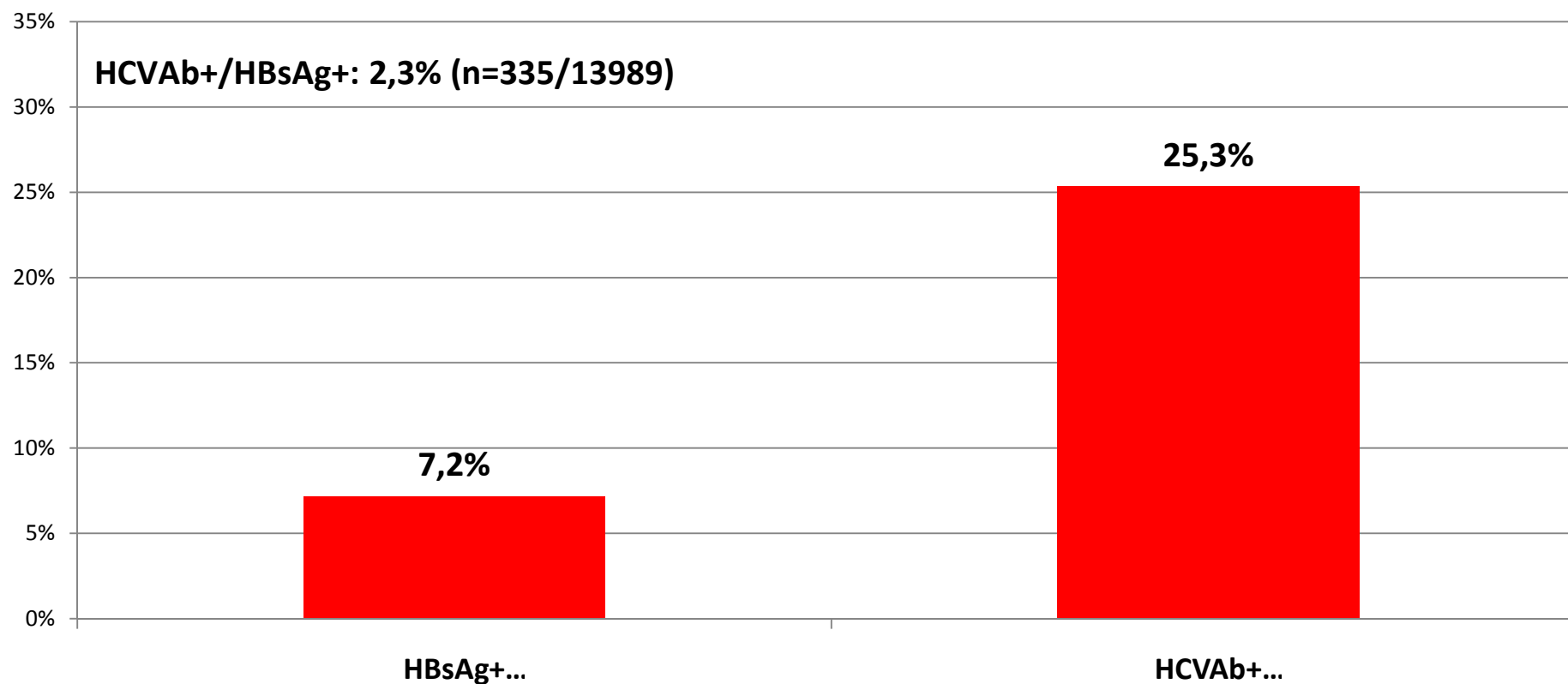
**excluding deaths among HIV+ people*

Prevalence of chronic hepatitis B among HIV-infected individuals.

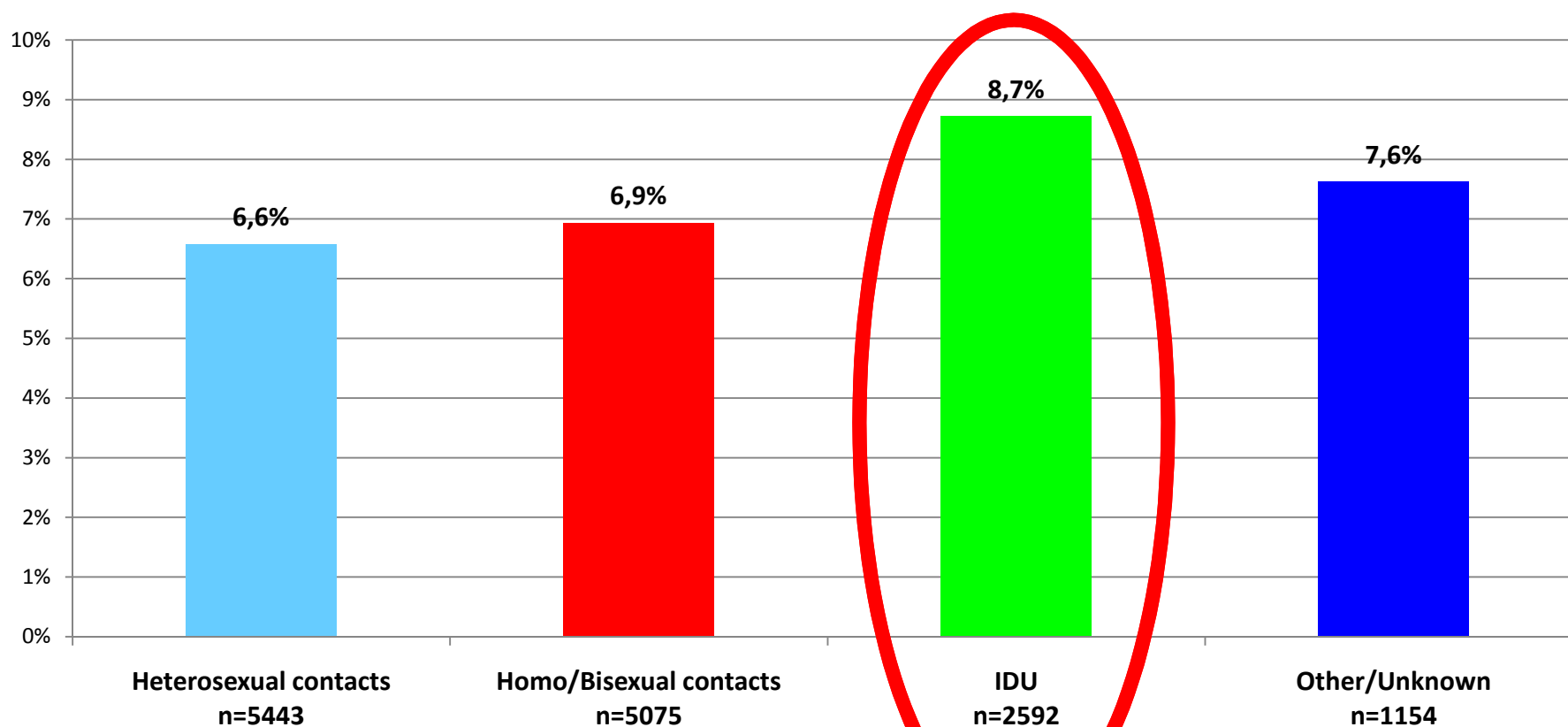
Prevalence rates reported in the last 5 years from studies that included a minimum of 100 HIV-infected individuals are shown in graduated colours. Many regions have not formally evaluated prevalence and

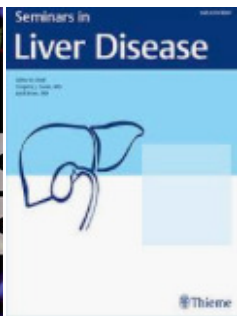


HBsAg and HCVAb positivity in 14.264 ICONA patients

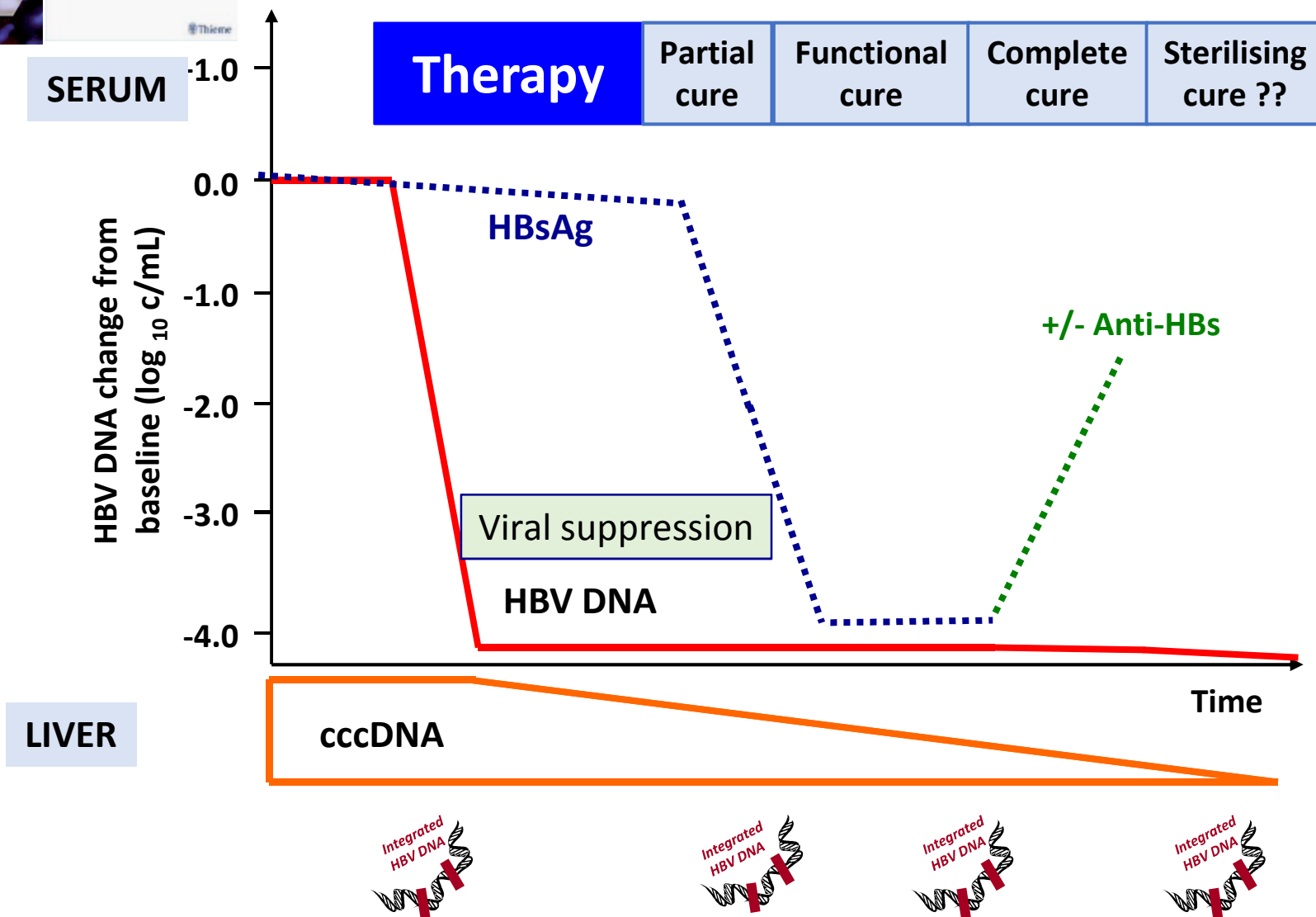


HBsAg positivity according to mode of HIV transmission in 14.264 ICONA patients





Definition of HBV cure: What do we want to achieve?



Background: ruolo dell'infezione HIV sull'Epatite B

Infezione HIV



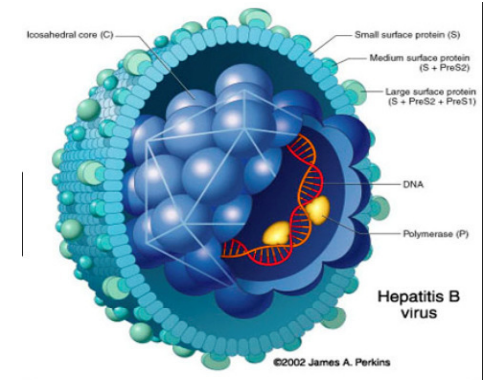
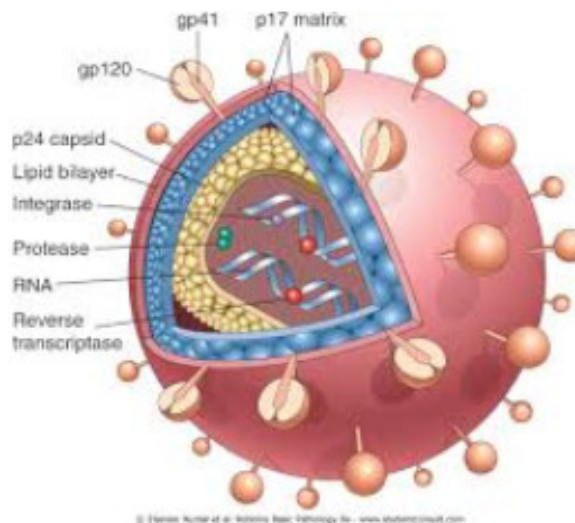
Deplezione Linfociti T
CD4+



Compromissione immunità
cellulo-mediata (ridotta
clearance virale) e umorale
(ridotta produzione di anticorpi)



Elevato rischio di
cronicizzazione dell'infezione
HBV e sierologia atipica di
infezione occulta (OBI)



- Incremento di replicazione di HBV
- Perdita di Anti-HBs
- Aumentato rischio di evoluzione in HCC, cirrosi e ESLD



HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS)

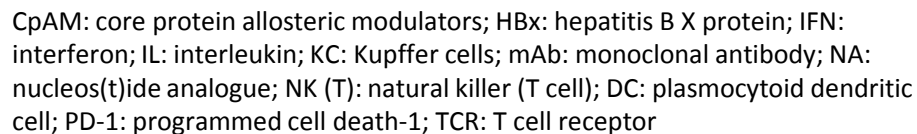
Comparison of liver-related mortality by HIV-1 and HBsAg status

HIV-1	HBsAg	Person years	Deaths from liver disease (n)	Liver mortality per 1000 person years	p
–	–	31 366	0	0·0	Reference
–	+	1318	1	0·8	0·04
+	–	20 605	35	1·7	<0·0001
+	+	1834	26	14·2	<0·0001
Overall		55 123	62	1·1	..

Rate of liver-related death also increased as the nadir CD4 count fell from more than 250 cells/L to less than 100 cells/L

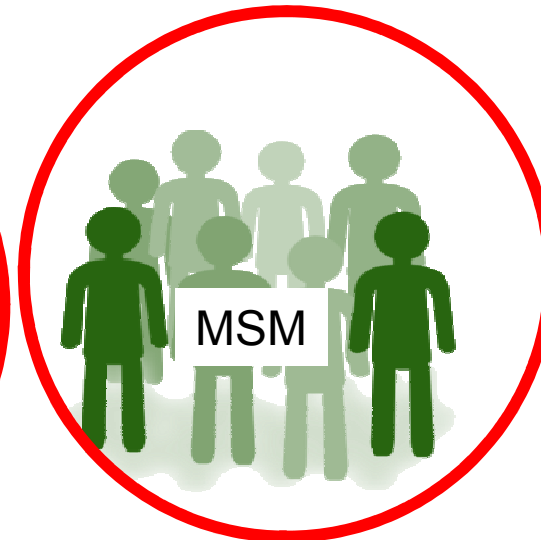
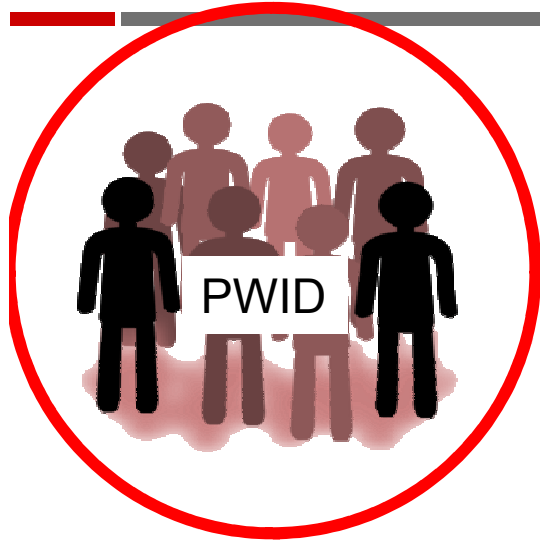
CD4 count, nadir (cells/ μ L)	HBsAg negative		HBsAg positive		HBsAg relative risk* (95% CI)
	Deaths/person years	Mortality rate per 1000 person years	Deaths/person years	Mortality rate per 1000 person years	
>250	10/13 938	0·7	6/1232	4·9	6·8 (2·0–20·6)
101–250	11/4260	2·6	10/441	22·7	8·8 (3·3–22·8)
<100	13/2370	5·5	10/157	63·6	11·6 (4·6–28·7)

Chloe L Thio et al. Lancet 2002



Overview of HCV

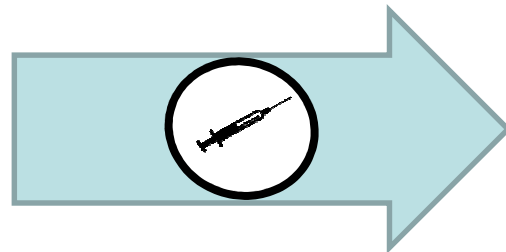
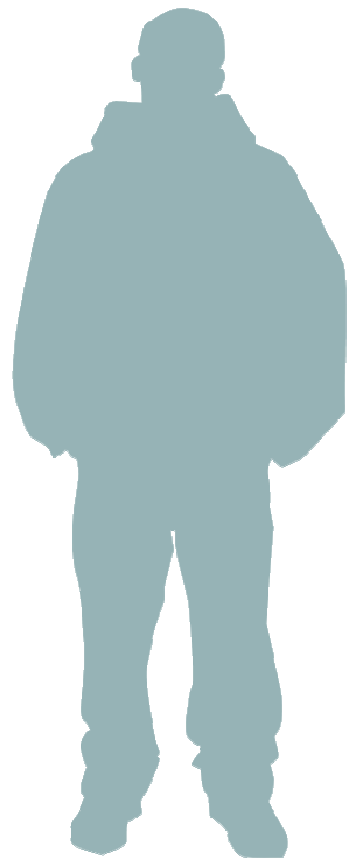
Vulnerable populations are disproportionately affected by HCV infection



MSM: men who have sex with men;
PWID: people who inject drugs

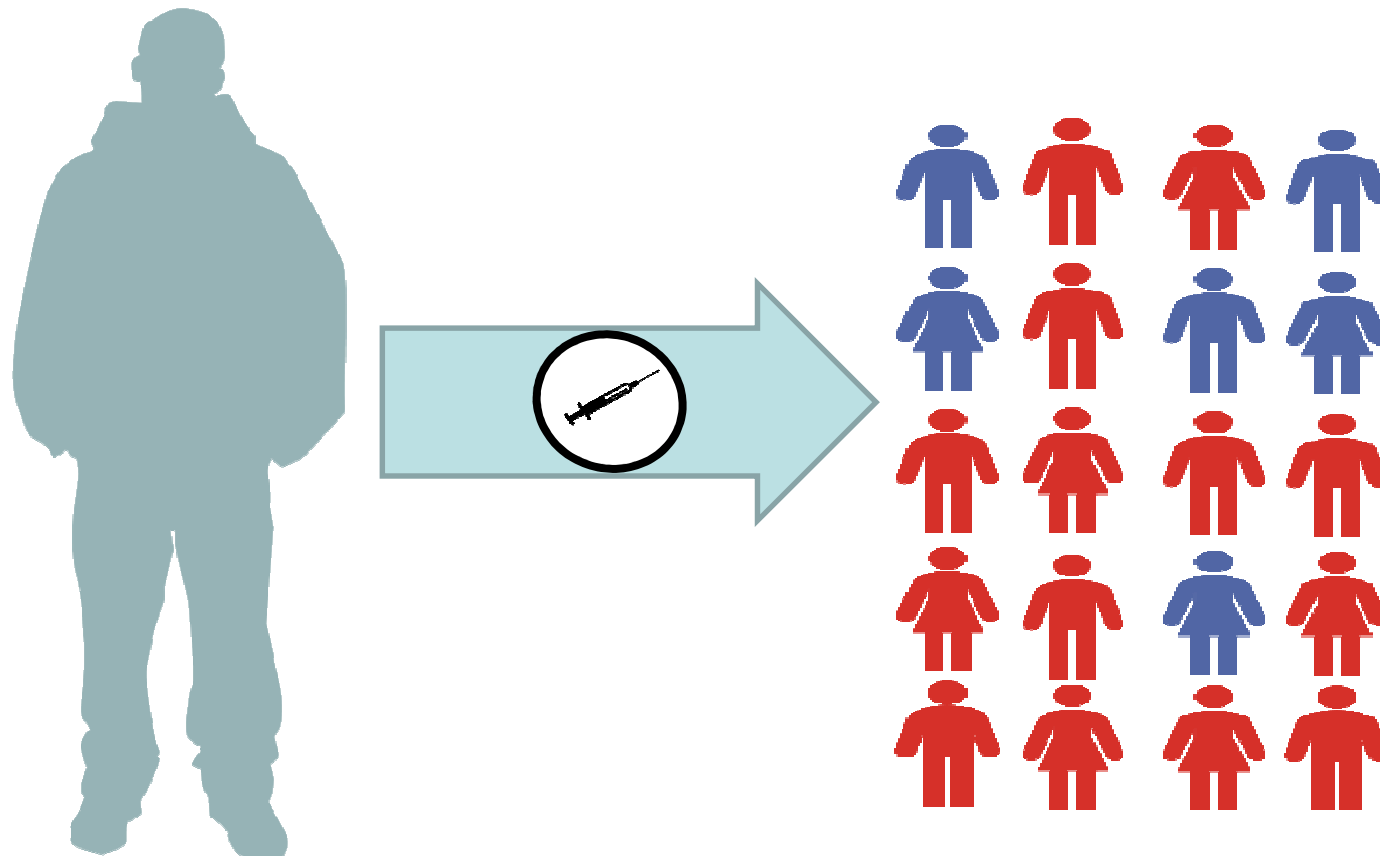


The Majority of New Cases Occur in PWID



**80% of new infections
occur among current
PWID**

HCV in PWID is a public health concern

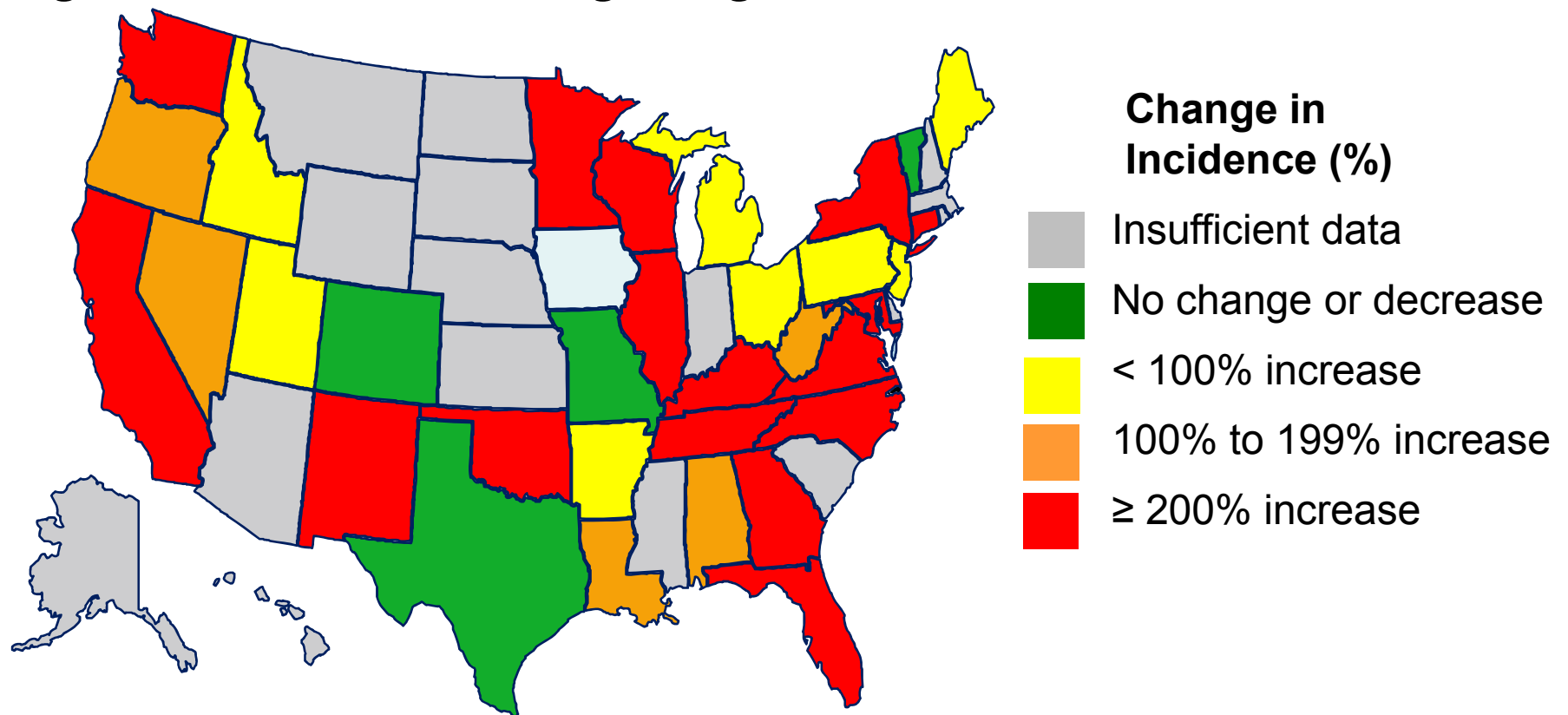


Each PWID infected with HCV is likely to infect about 20 others within the first 3 years of initial infection

Opioid Epidemic Is Increasing HCV Transmission

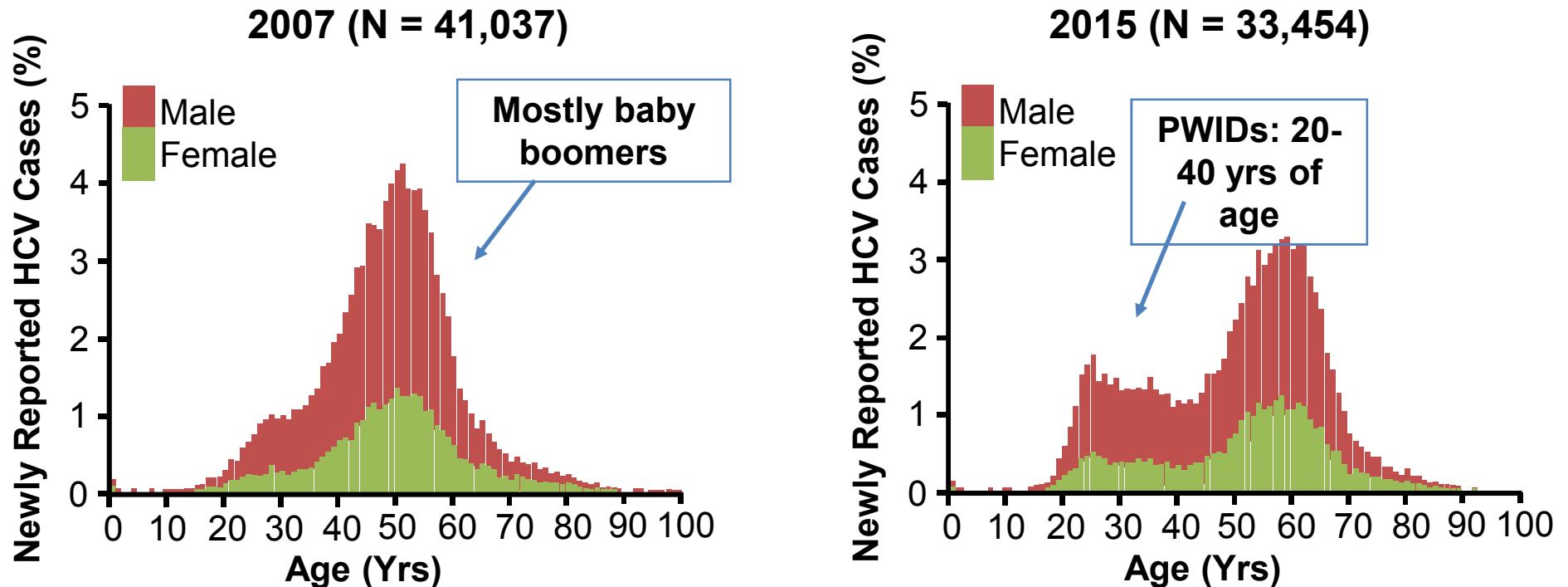
- Increase in new HCV infections in the US is primarily among young white adults with injection drug use^[1]
 - Has led to increase in mother-to-child transmission^[2]

Change in HCV Incidence Among Young PWID, 2006-2012^[3]



1. Zibbel JE, et al. MMWR Morb Mortal Wkly Rep. 2015;64:453-458. 2. Koneru A, et al. 2016;65:705-710. 3. Suryaprasad AG, et al. Clin Infect Dis. 2014;59:1411-1419.

Changing Epidemiology of HCV in the US



- Screening → linkage to HCV care → DAA treatment cascade must be operative in all those at risk
- Treatment of PWIDs plus harm reduction efforts essential part of elimination efforts

California Department of Public Health. Chronic hepatitis C infections in California: cases newly reported through 2015. June 2017.

Injection drug use is a major route of HCV transmission

Route of transmission	HCV incidence	HCV prevalence
Intravenous drugs	5.2–42 per 100 PY* ¹	Globally 67% ²
Sexual transmission in HTX monogamous	0.036–0.072 per 100 PY ³	0.036–0.072 per 100 py ³
Sexual transmission in HIV+ MSM	0.53 per 100 PY ⁴	8.2% overall ⁵ 40% if also IDU ⁵
Vertical transmission		4% mono-infected mothers ⁶ 11% HIV co-infected mothers ⁶

- From 1992, very little iatrogenic or nosocomial HCV transmission in developed countries, but high occurrence in low income countries prevails⁷

1. Wiessing L, et al. PLoS One 2014;9:e103345; 2. Grebely J, et al. Antiviral Res 2014;104:62–72; 3. Terrault N, et al. Hepatology 2013;57:881–9; 4. Hagan H, et al. AIDS 2015;29:2335–45; 5. Jordan AE, et al. Int J STD AIDS 2017;28:145–59; 6. Muñoz-Almagro C, et al. Med Clin (Barc) 2002;12:452–4; 7. Shepard CW, et al. Lancet Infect Dis 2005;5:558–67

*Current or recent injectors.
HTX: heterosexual; IDU: injecting drug user;
MSM: men who have sex with men; PY: person-years

VIRAL HEPATITIS

Incidence and Prevalence of Hepatitis C in Prisons and Other Closed Settings: Results of a Systematic Review and Meta-Analysis

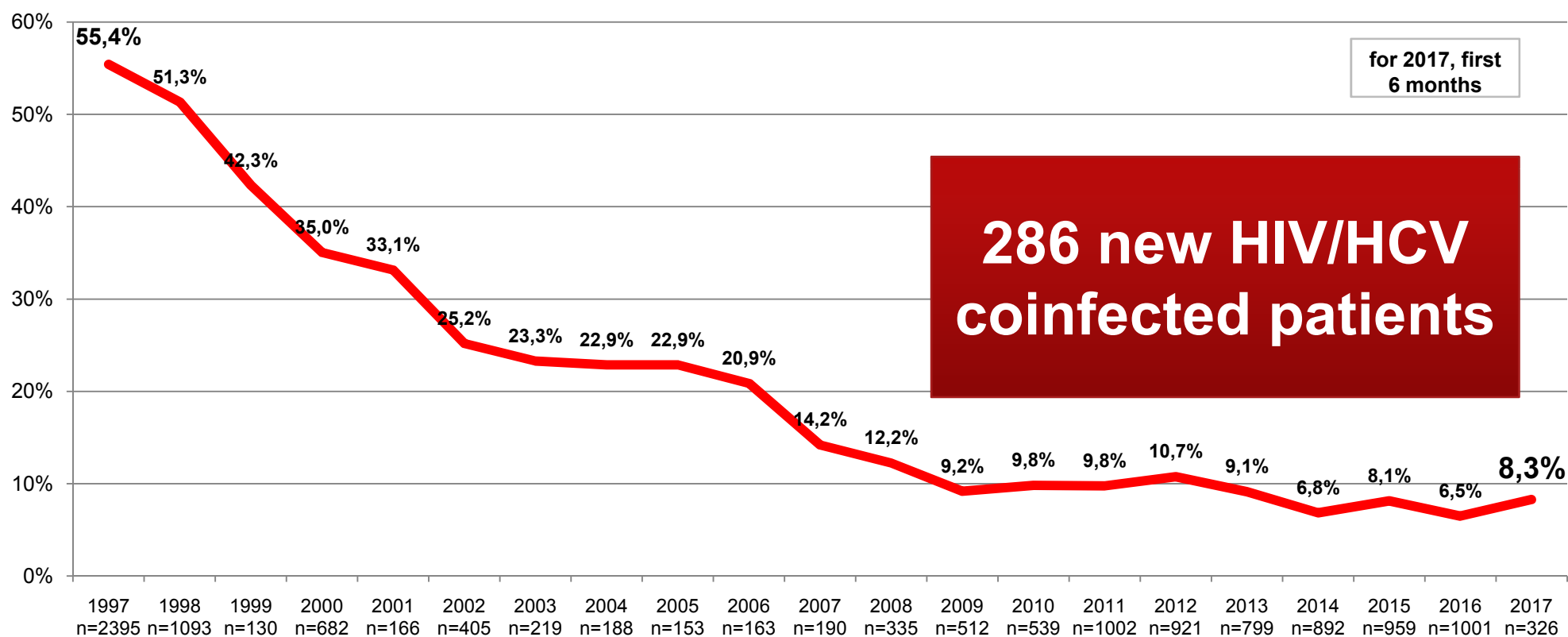
Prevalence of anti-HCV

**General detainees was 26%,
Detainees with a history of IDU, 64%**

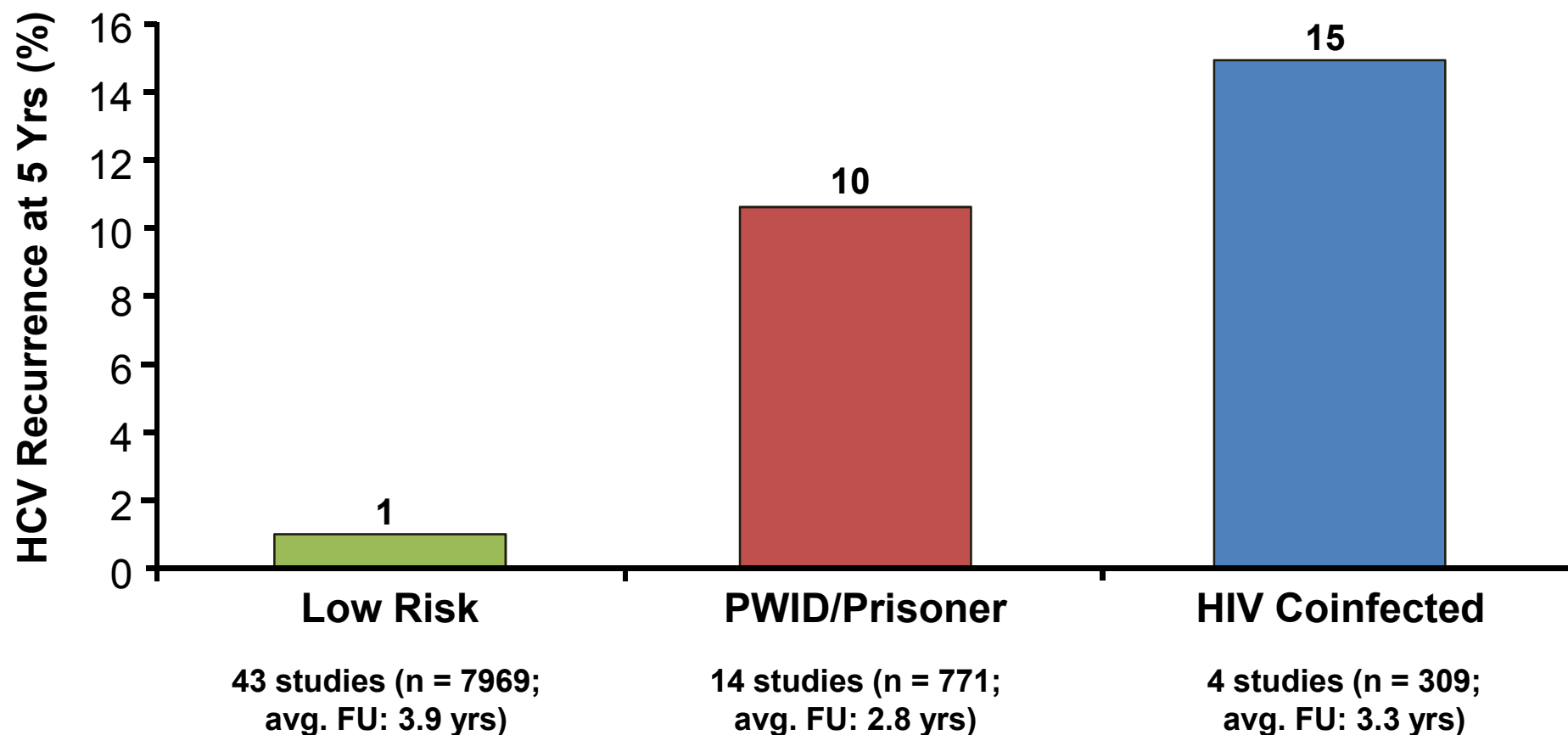
HCV incidence

**General detainees was 1.4 per 100 person-years,
detainees with a history of IDU was 16.4 per 100 py.**

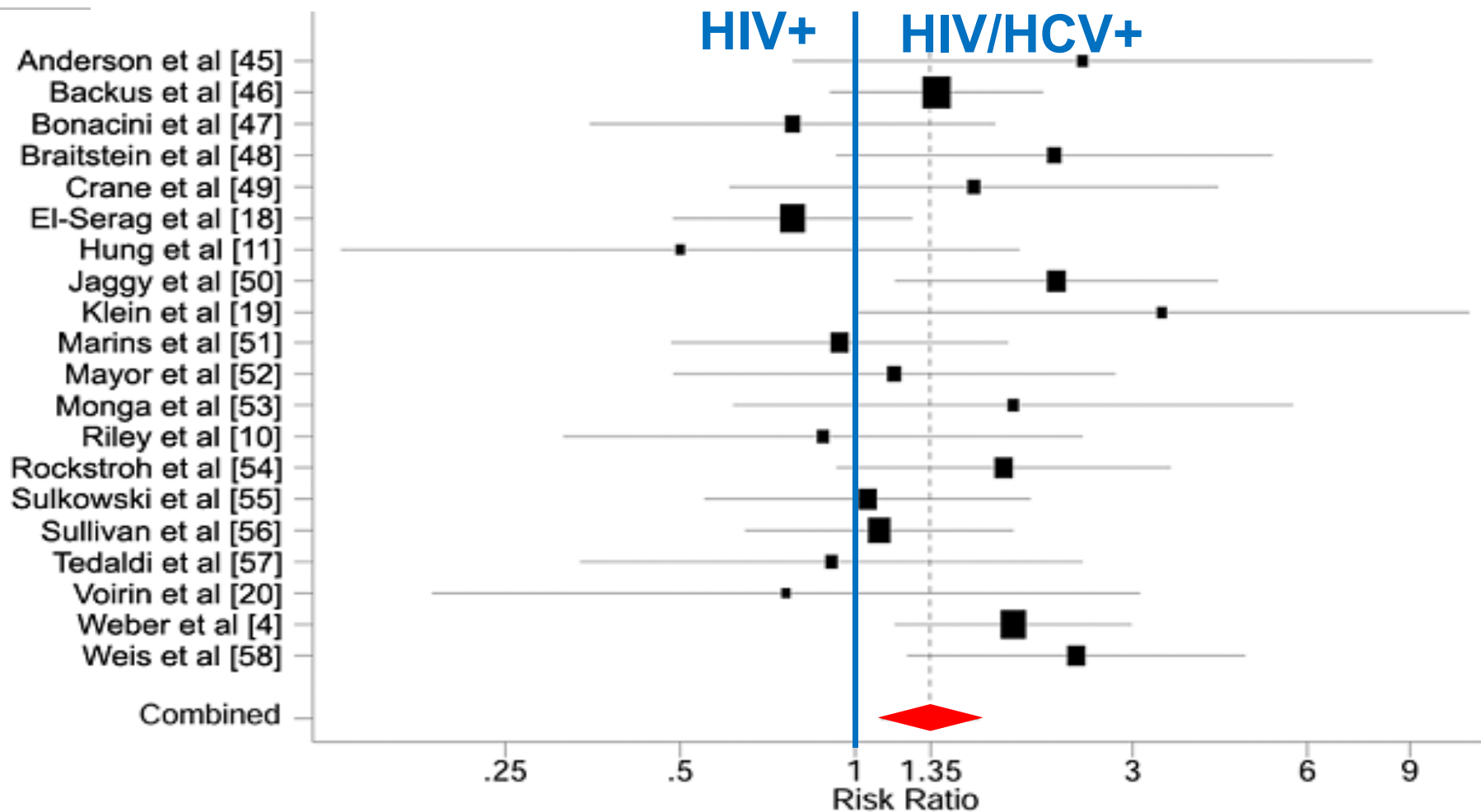
Proportion of patients with HCVAb pos test within 1 year from enrolment, according to calendar year of enrolment



HCV Reinfection Over 5 Yrs by Study Population

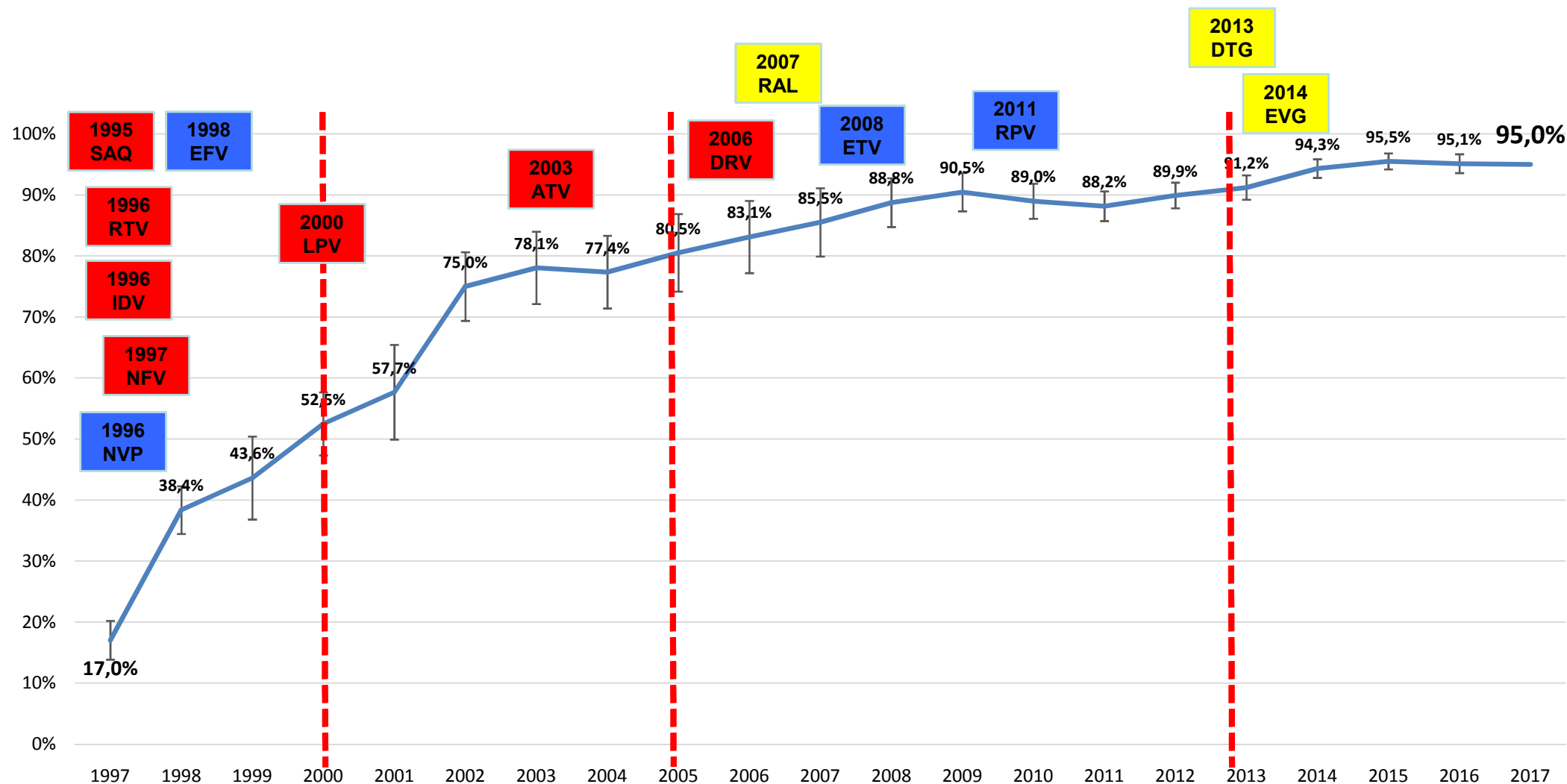


HCV coinfection increases overall mortality

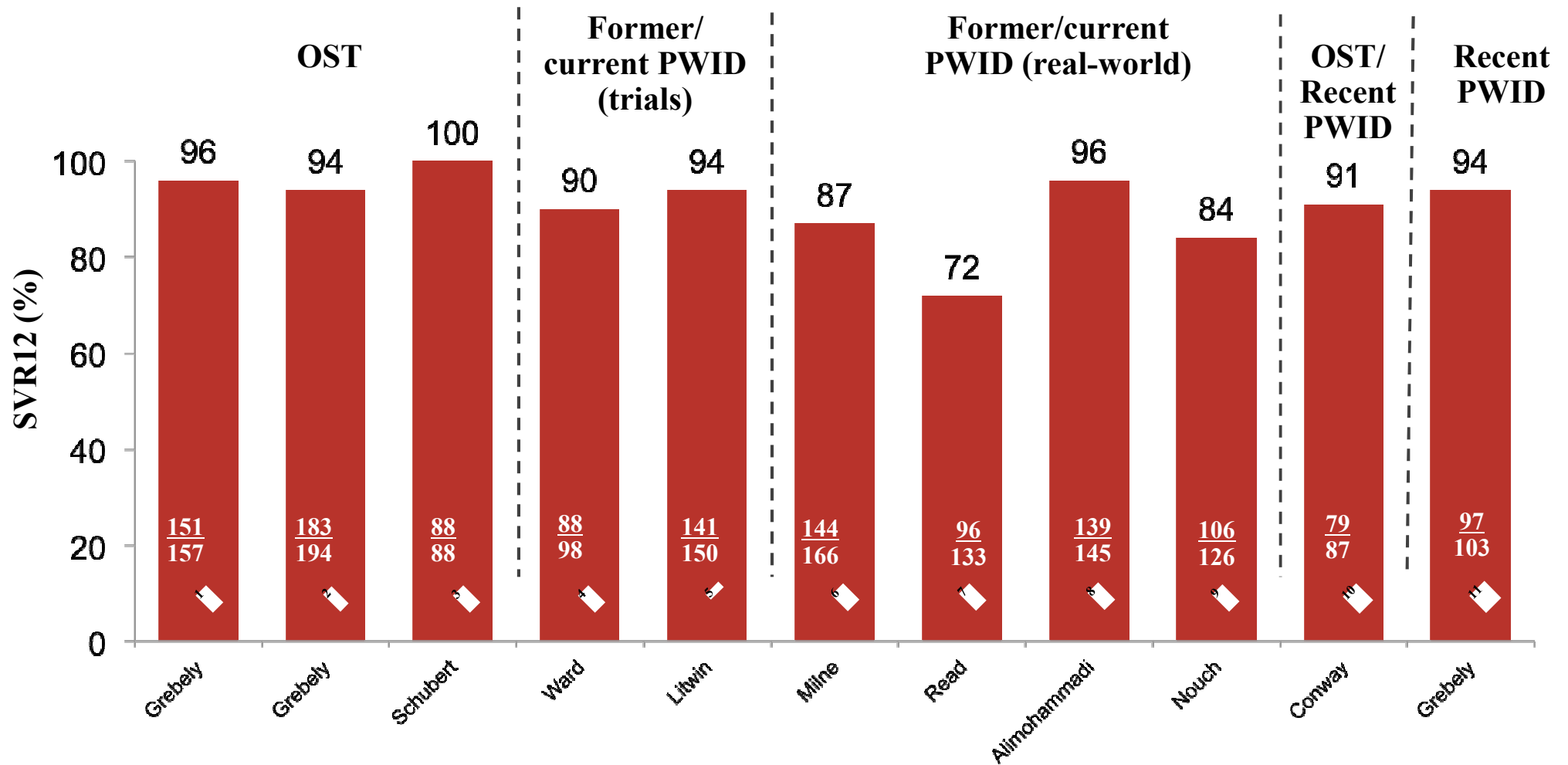


Overall mortality, HAART era

Proportion of patients with a VL $\leq$ 80 copies/mL at 12 months from starting their first ART regimen by calendar year of initiation



HCV DAA Therapy Among People on OST and PWID



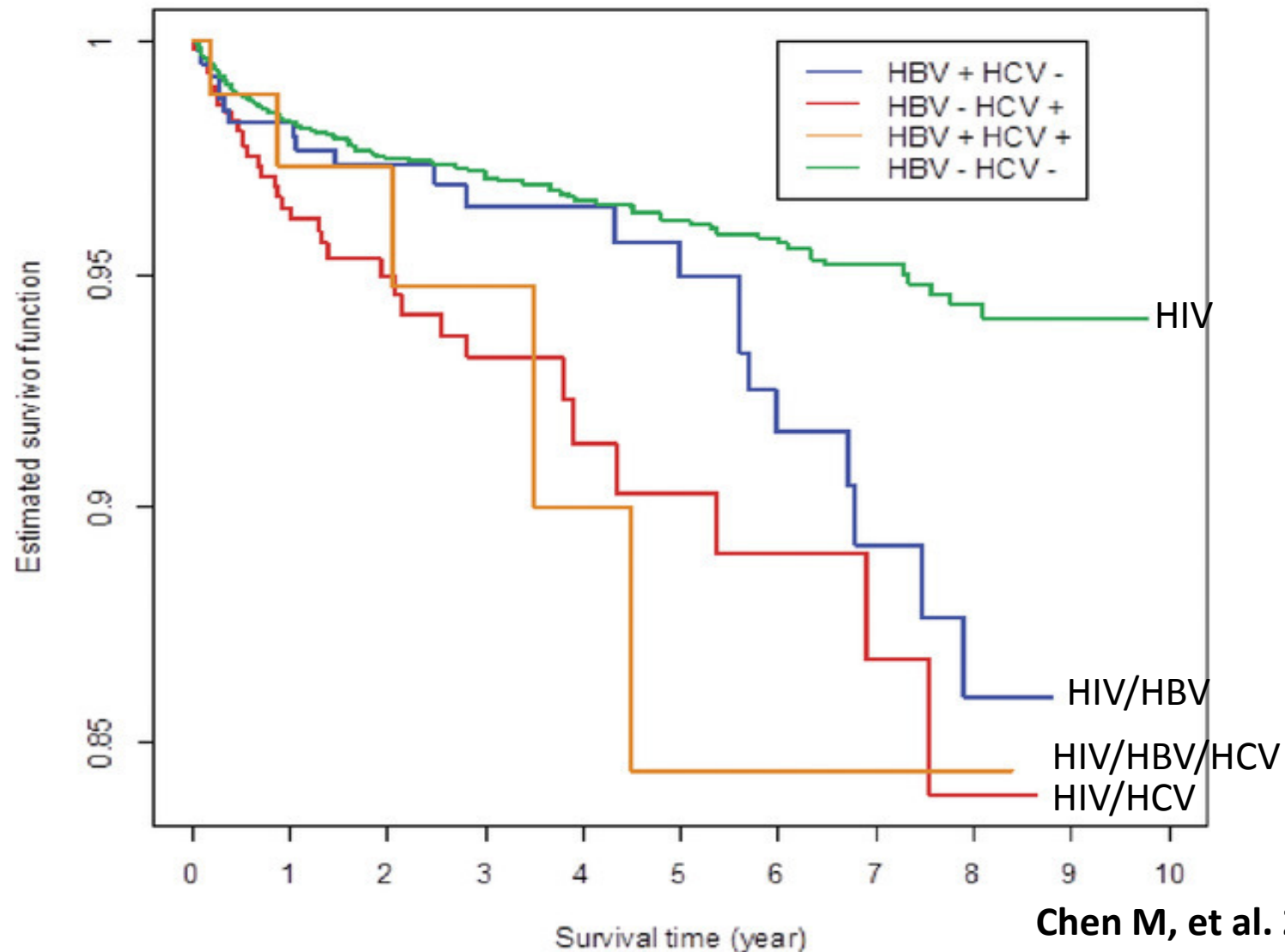
HCV Therapy in HIV/HCV-Co-infected Patients

Study	Population	HCV Regimens	SVR12, %
ION-4 ^[1]	N = 335; GT1 (98%) or 4	LDV/SOF 12 wks	96
TURQUOISE-II ^[2]	N = 63; GT1	OBV/PTV/RTV + DSV + RBV 12 wks	94
		OBV/PTV/RTV + DSV + RBV 24 wks	91
ALLY-2 ^[3]	N = 151; GT1 (83%), 2, 3, or 4	Tx-naive:	
		▪ SOF + DCV 12 wks	97
		▪ SOF + DCV 8 wks	76
		Tx-expd: SOF + DCV 12 wks	98
C-EDGE ^[4]	N = 218; GT1, 4 or 6	Elbasvir + Grazoprevir 12 w	96
NIH ^[5]	N = 50; GT1	LDV/SOF 12 wks	98
SIMIT ^[6]	N = 210 GT1	OBV/PTV/RTV + DSV ± RBV 12 wks	97

1. Naggie S, et al. N Engl J Med. 2015;373:705-713. 2. Sulkowski MS, et al. JAMA. 2015;313:1223-1231.
3. Wyles DL, et al. N Engl J Med. 2015;373:714-725. 4. Rockstroh JK, et al. Lancet. 2015; 2:319-27.
5. Osinusi A, et al. JAMA. 2015;313:1232-1239. 6. Andreoni M et al CID 2016 in press

Overall survival by HBV or HCV co-infection status in 7,455 subjects.

TREAT Asia HIV Observational Database



Chen M, et al. 2016



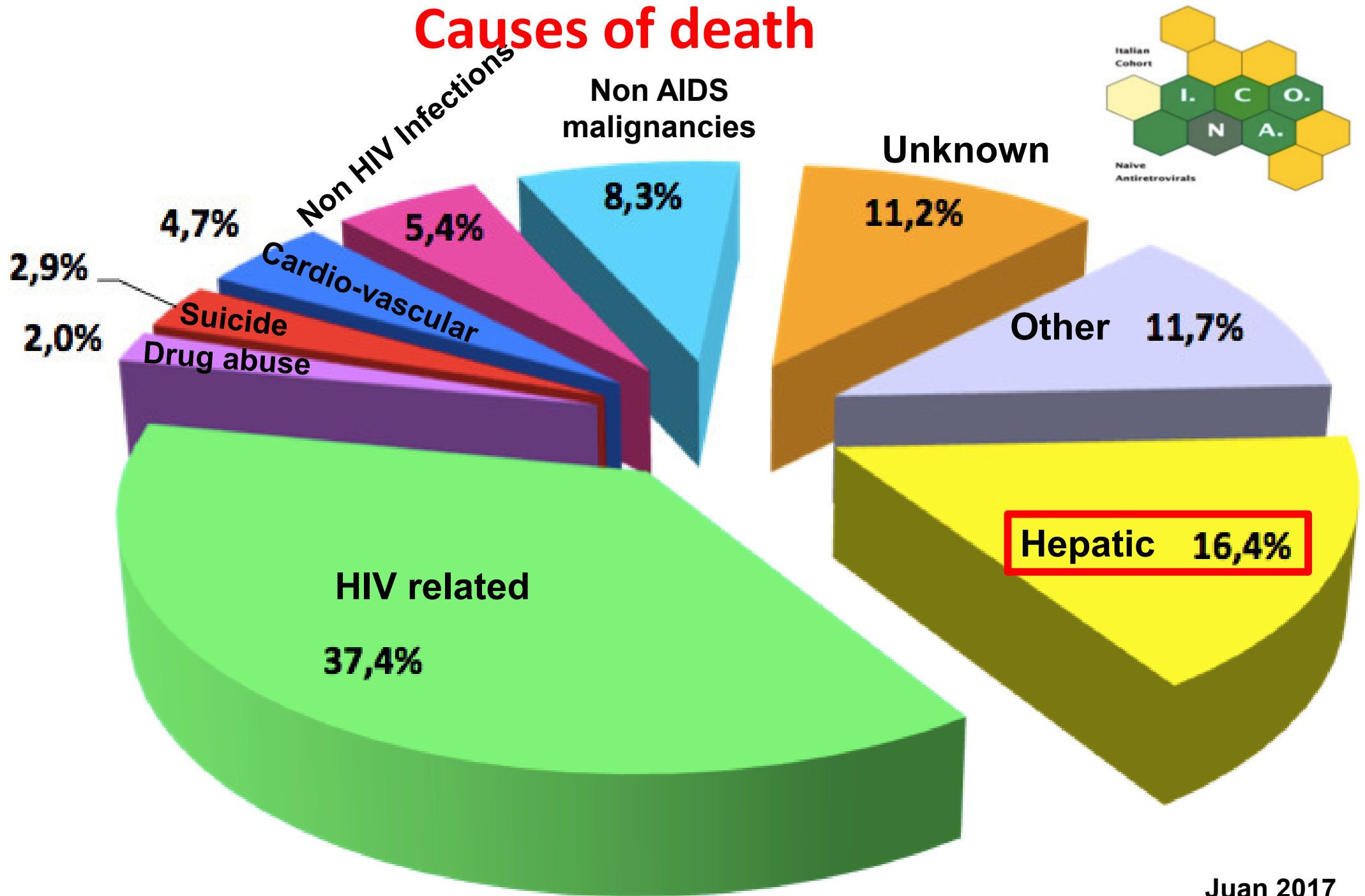
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Causes of death





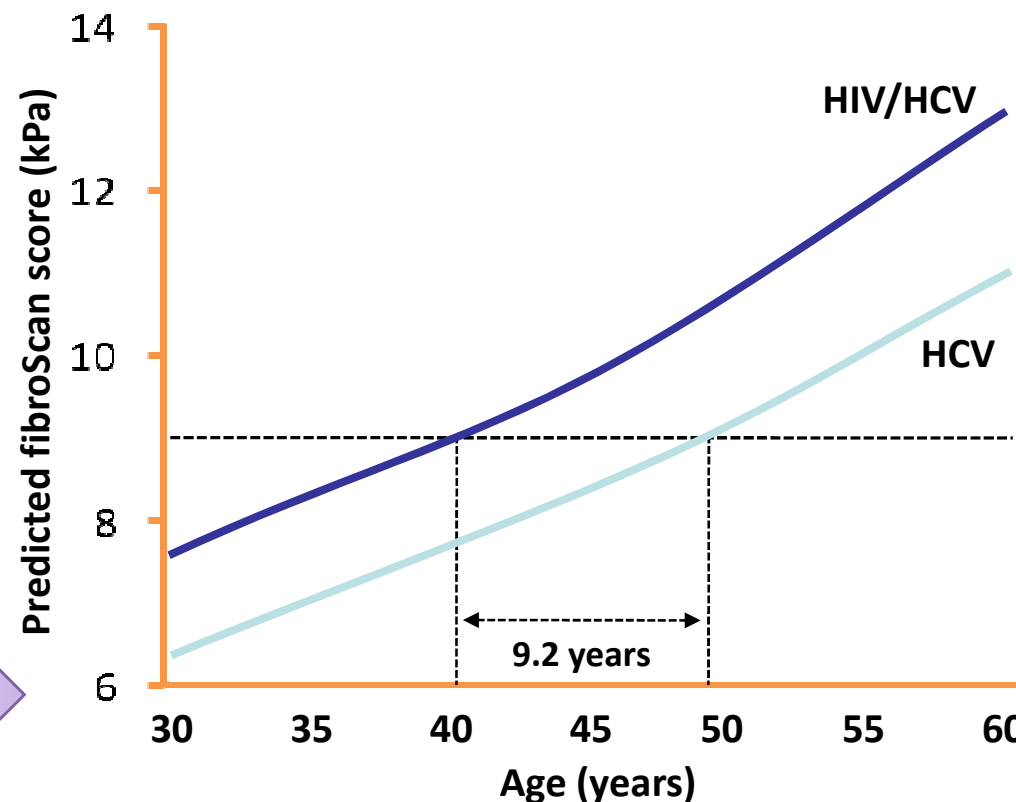
ALIVE Study: HIV, Age, and Severity of HCV-Related Liver Diseases

Liver fibrosis and age:
HIV/HCV versus HCV infection

Prospective cohort of 1176
HCV-infected IDUs, including 394 patients
co-infected with HIV

Fibrosis was significantly greater in
HIV/HCV co-infected versus HCV mono-
infection ($P < 0.001$)

HIV/HCV co-infected patients have liver
fibrosis similar to HCV
mono-infected patients who
are nearly 10 years older



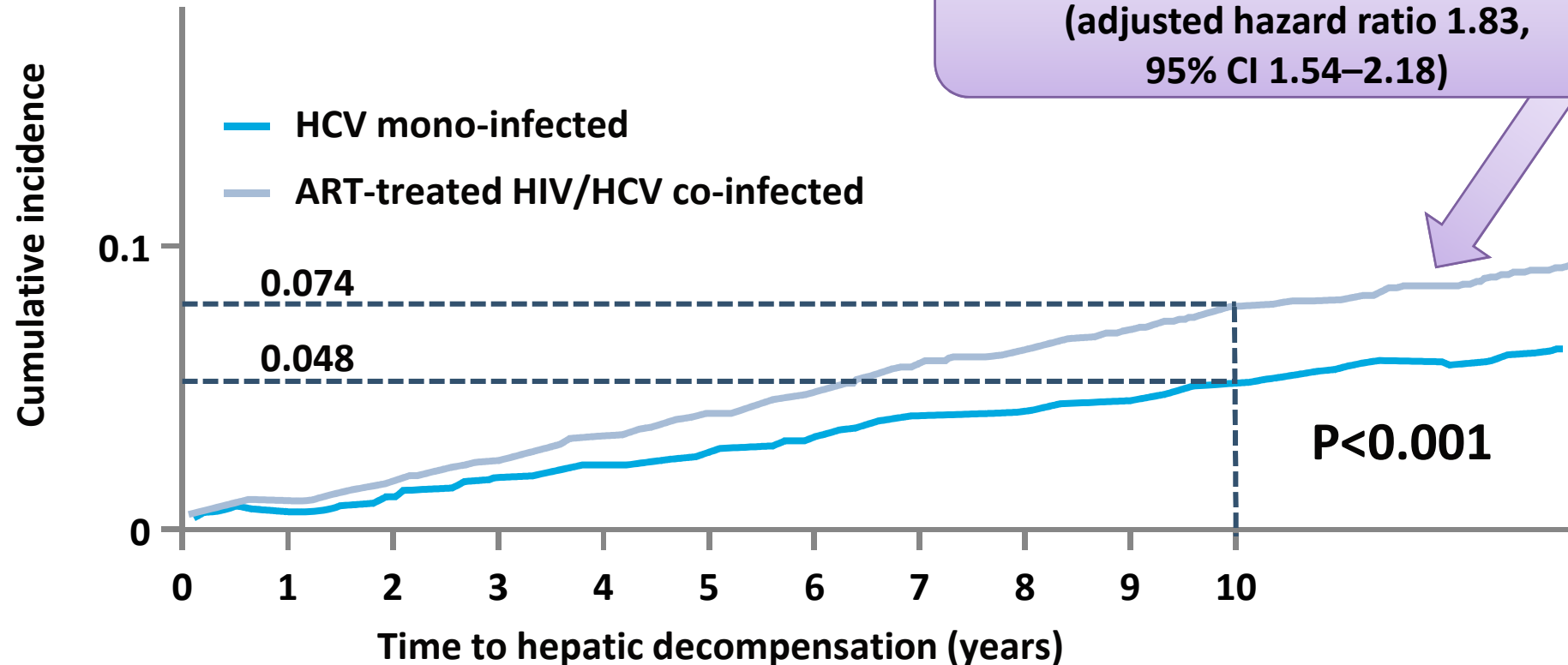
ALIVE = AIDS Linked to the IntraVenous Experience; IDU = injection drug user.

Kirk GD, et al. *Ann Intern Med* 2013; 158:658-666.



The Risk of Hepatic Decompensation* is Higher in HCV-Infected Patients who are Co-infected With HIV

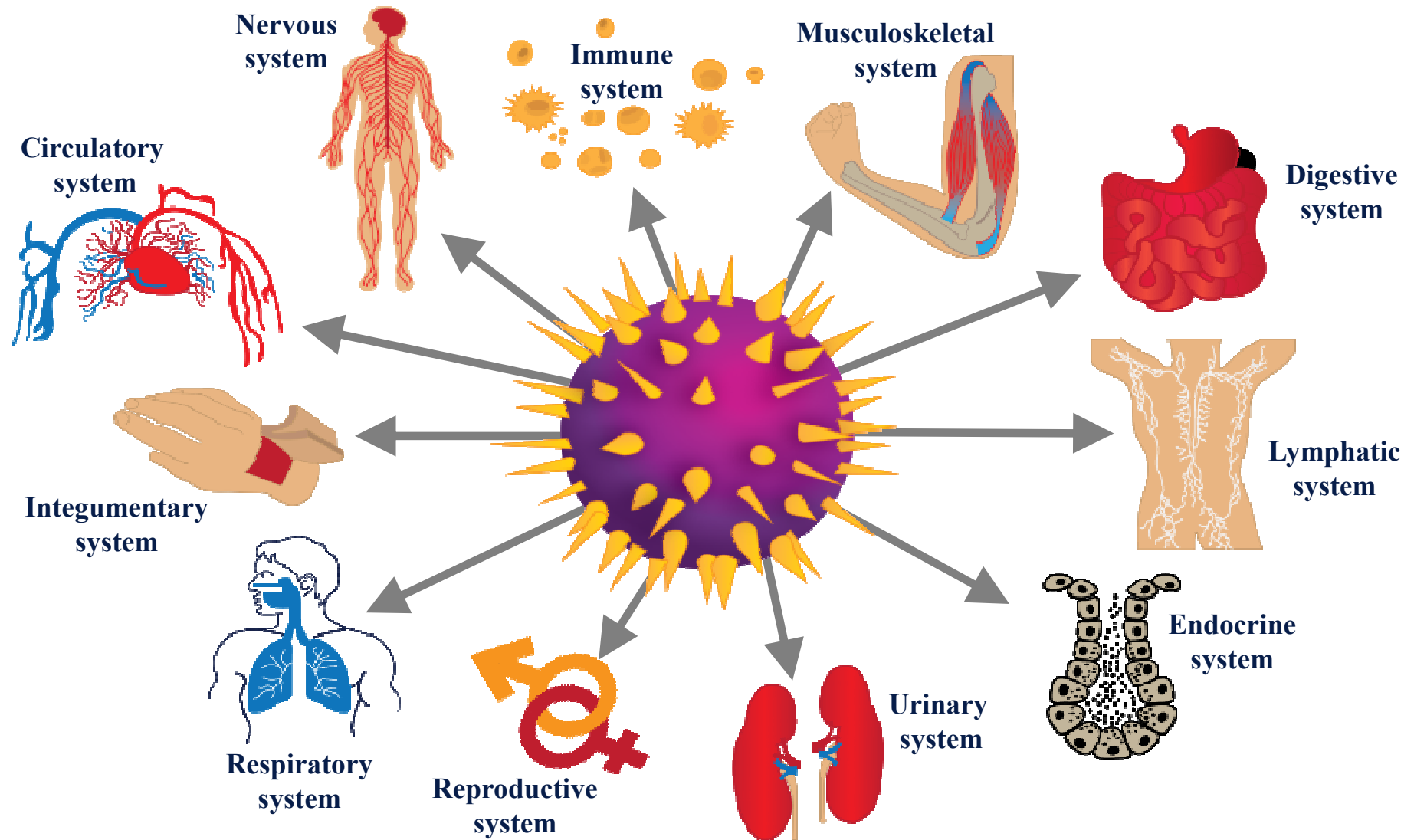
Hepatic decompensation risk is higher in the co-infected group (adjusted hazard ratio 1.83, 95% CI 1.54–2.18)



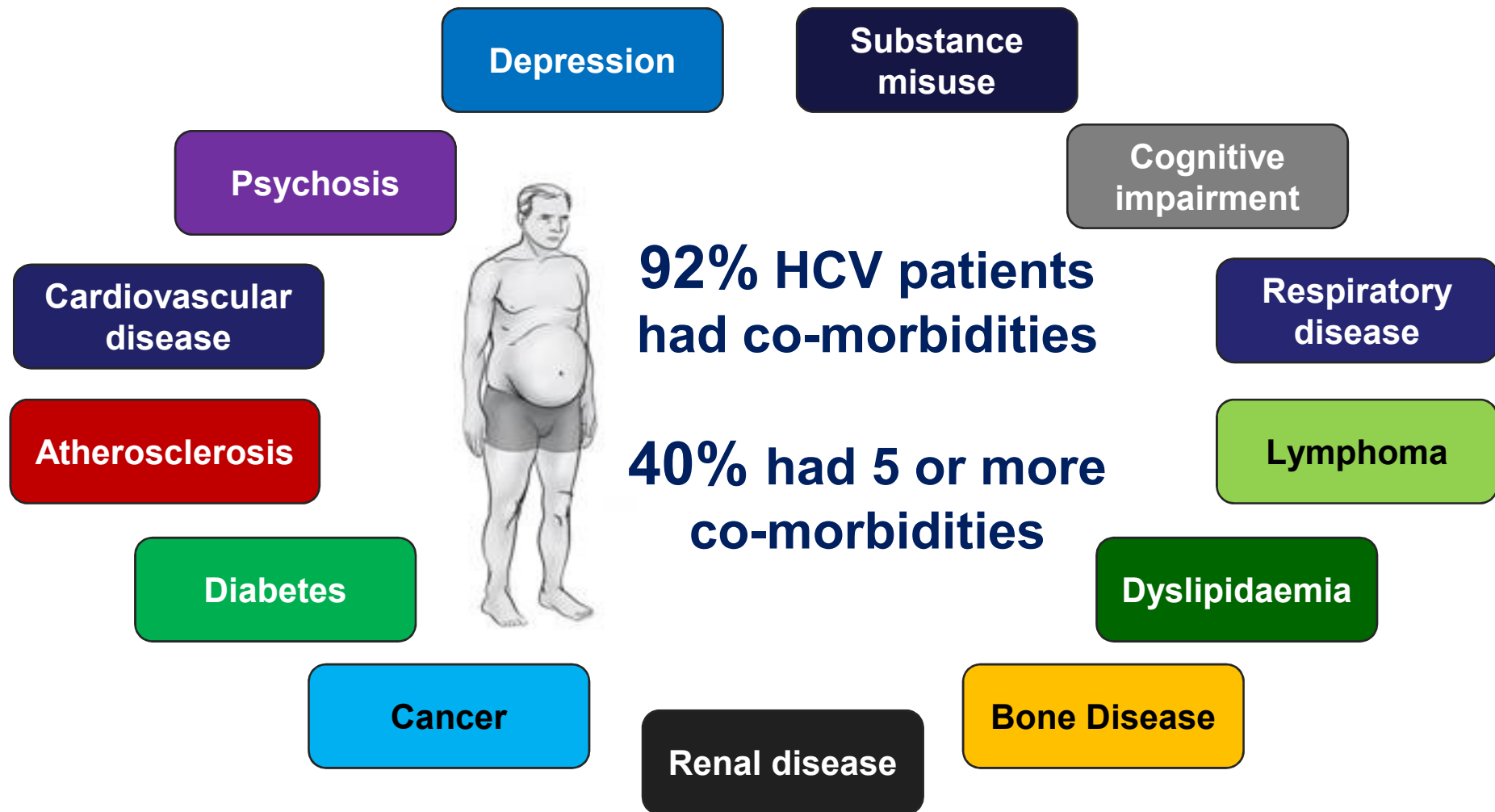
ART = antiretroviral treatment.

* The primary outcome was incident hepatic decompensation, which was defined by one hospital discharge ICD-9 diagnosis or two or more outpatient ICD-9 diagnoses of ascites, spontaneous bacterial peritonitis, or esophageal variceal hemorrhage in the Veterans Aging Cohort Study Virtual Cohort.

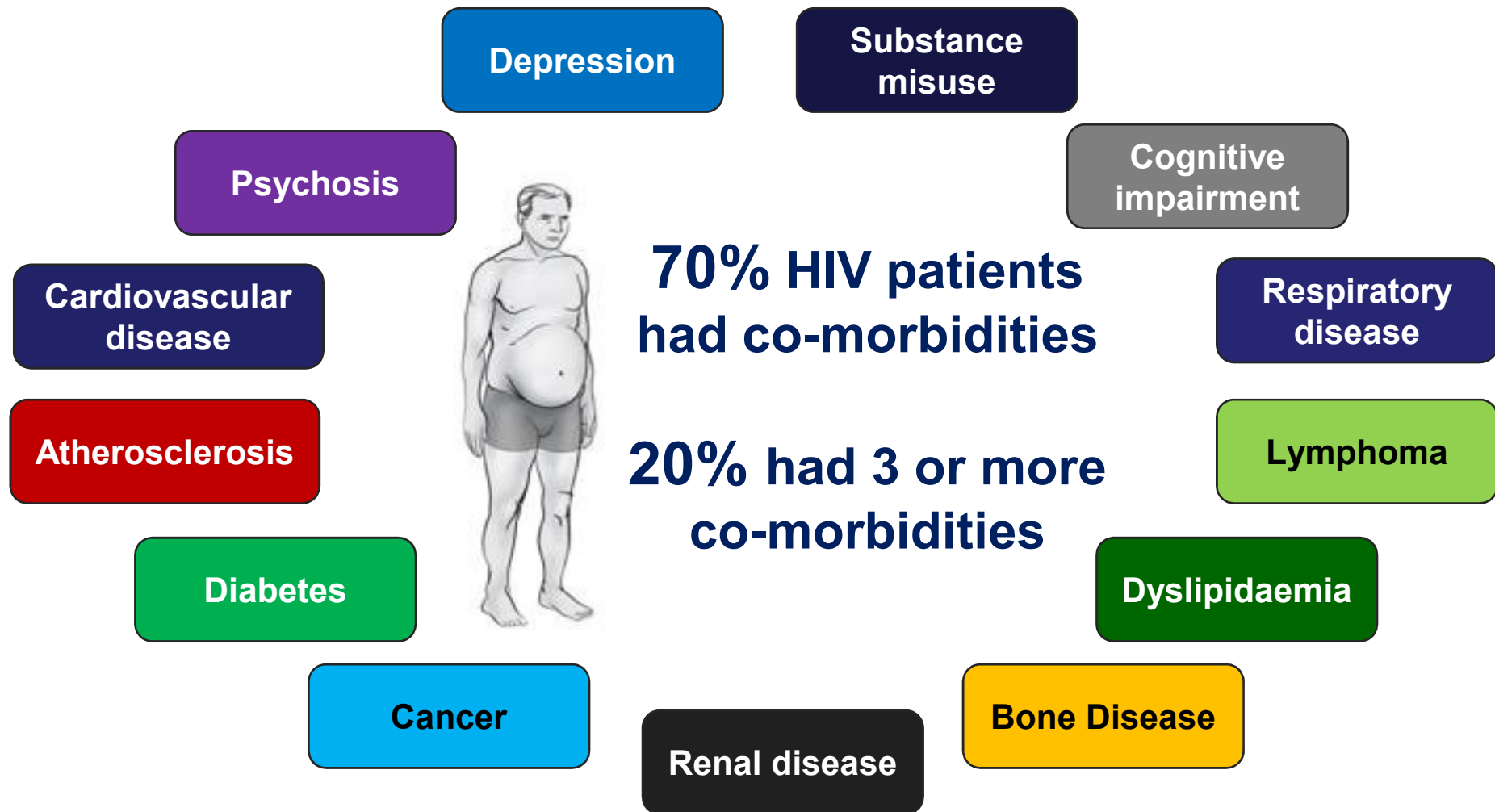
HIV and HCV are two Systemic Infections Affecting Multiple Body Systems Beyond the Liver



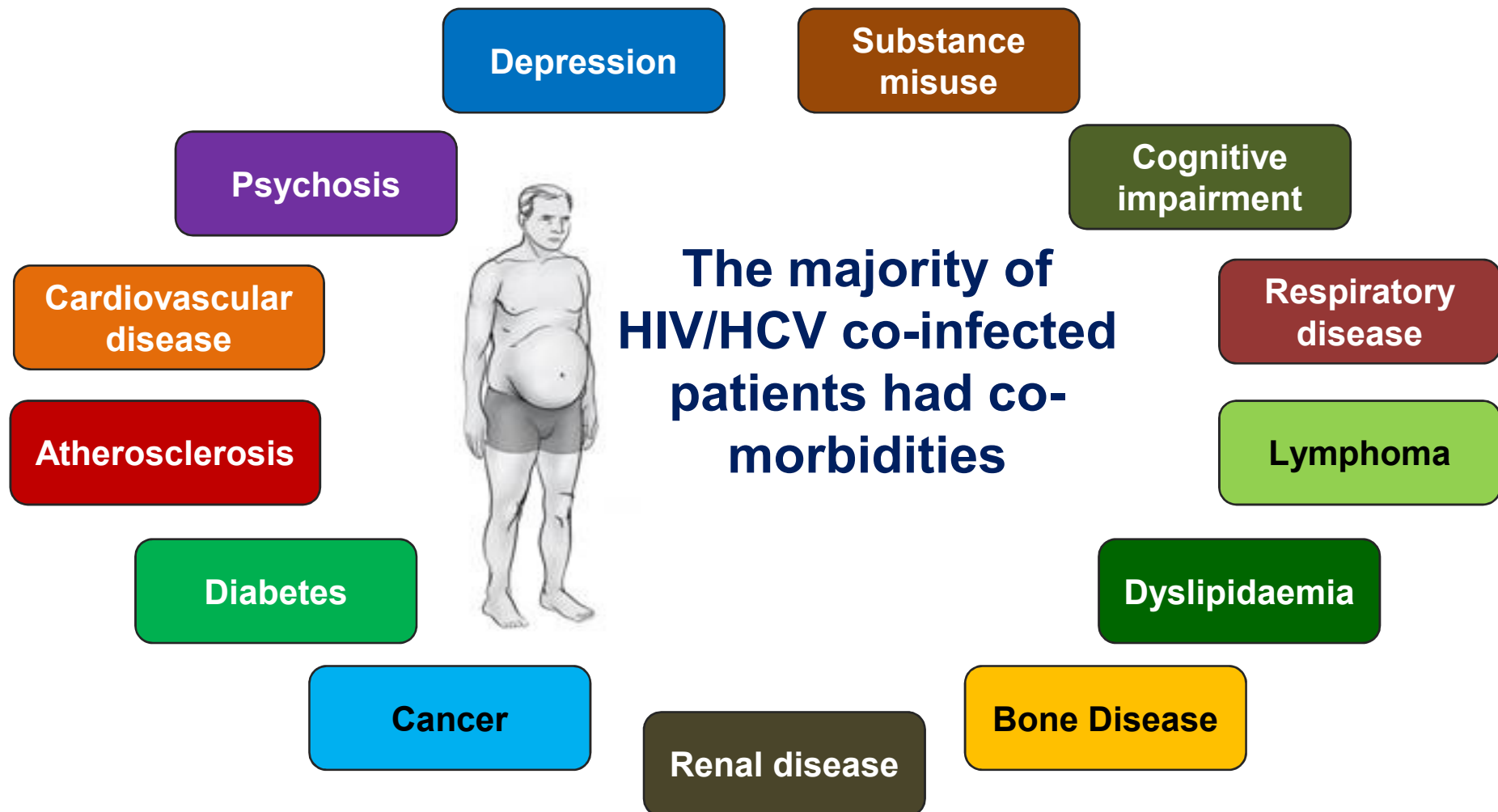
Co-morbidities in HCV patients are relevant – bringing potential for competing risks



Co-morbidities in HIV patients are relevant – bringing potential for competing risks

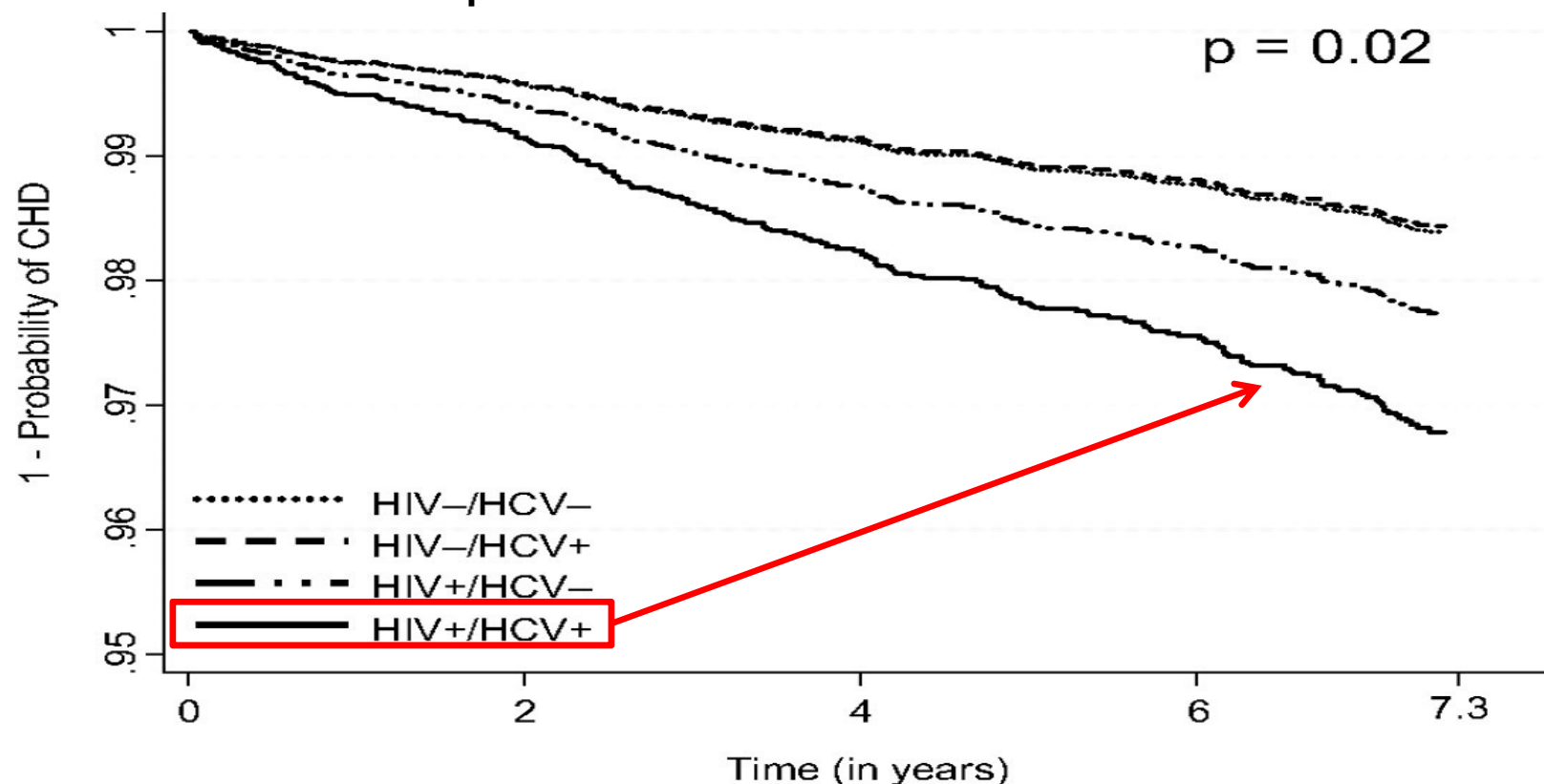


Co-morbidities in HIV/HCV co-infected patients are relevant



Frailty of HIV/HCV co-infected patient: cardiovascular issues

Adjusted survival curves from Cox proportional hazard models among HIV+HCV+, HIV+HCV-, HIV-HCV+, and HIV-HCV- Veterans and the risk of CHD. Solid line represents the risk for HIV+HCV+ Veterans.



No. at risk

HIV-/HCV-	5453	5212	4898	4435	2918
HIV-/HCV+	701	685	648	575	398
HIV+/HCV-	1687	1532	1379	1208	932
HIV+/HCV+	738	655	566	477	353



HCV Co-infection is Associated with an Increased Risk of Chronic Kidney Disease Progression in Patients with HIV

CKD outcomes from 52,602 HCV seronegative, 9,508 HCV viremic and 913 HCV aviremic HIV-infected subjects from NA-ACCORD

Stage 3 CKD

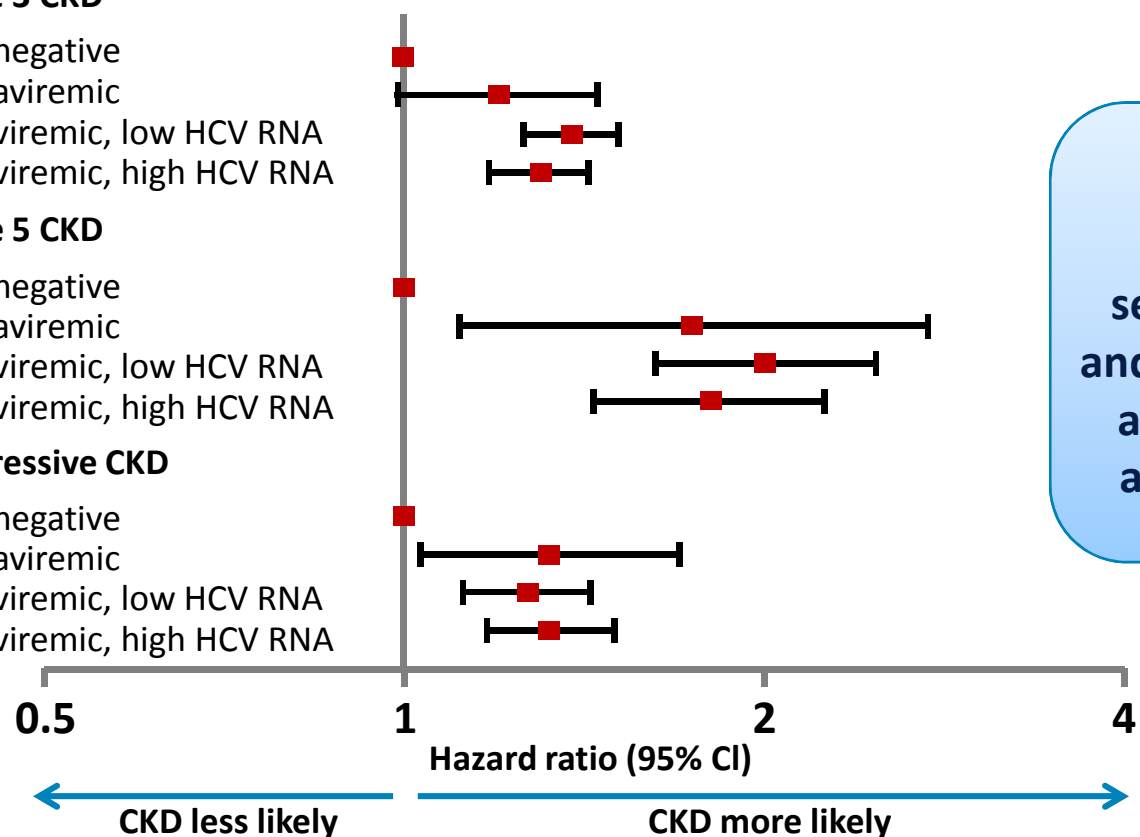
HCV negative
HCV aviremic
HCV viremic, low HCV RNA
HCV viremic, high HCV RNA

Stage 5 CKD

HCV negative
HCV aviremic
HCV viremic, low HCV RNA
HCV viremic, high HCV RNA

Progressive CKD

HCV negative
HCV aviremic
HCV viremic, low HCV RNA
HCV viremic, high HCV RNA



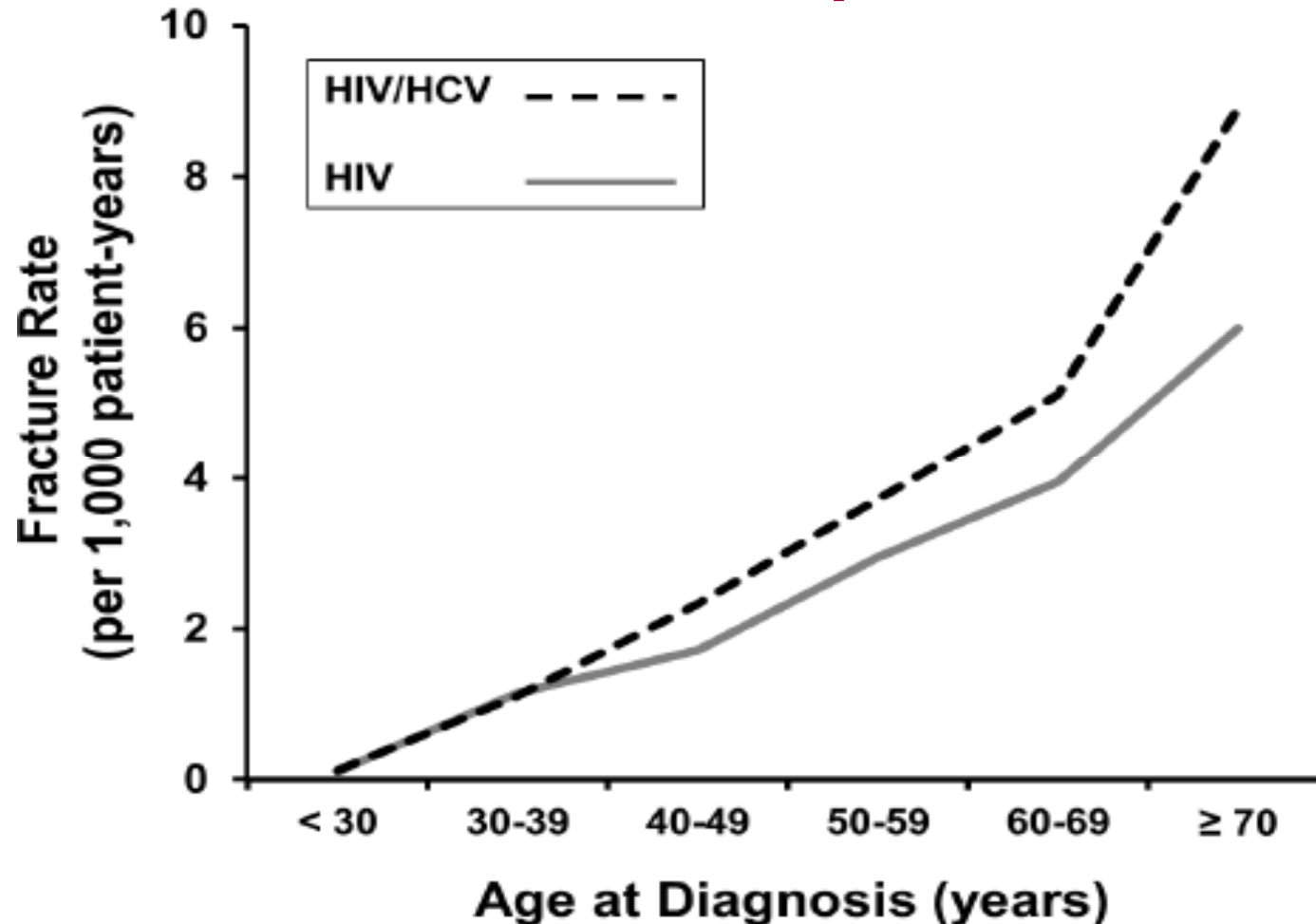
Compared with HIV-infected subjects who were HCV seronegative, both HCV viremic and HCV aviremic individuals were at increased risk for moderate, advanced and progressive CKD

CKD = chronic kidney disease; HCV viremic = detectable HCV RNA; HCV aviremic = HCV seropositive, undetectable HCV RNA; NA-ACCORD = North American AIDS Cohort Collaboration on Research and Design.

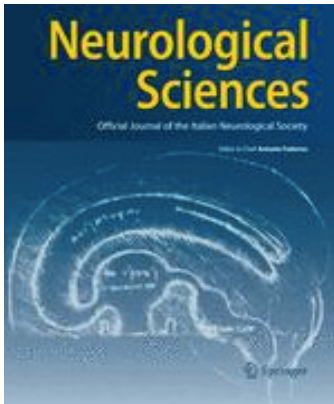
Lucas GM, et al. *J Infect Dis* 2013; 208:1240–1249.



Hepatitis C co-infection and severity of liver disease as risk factors for osteoporotic fractures among HIV-infected patients

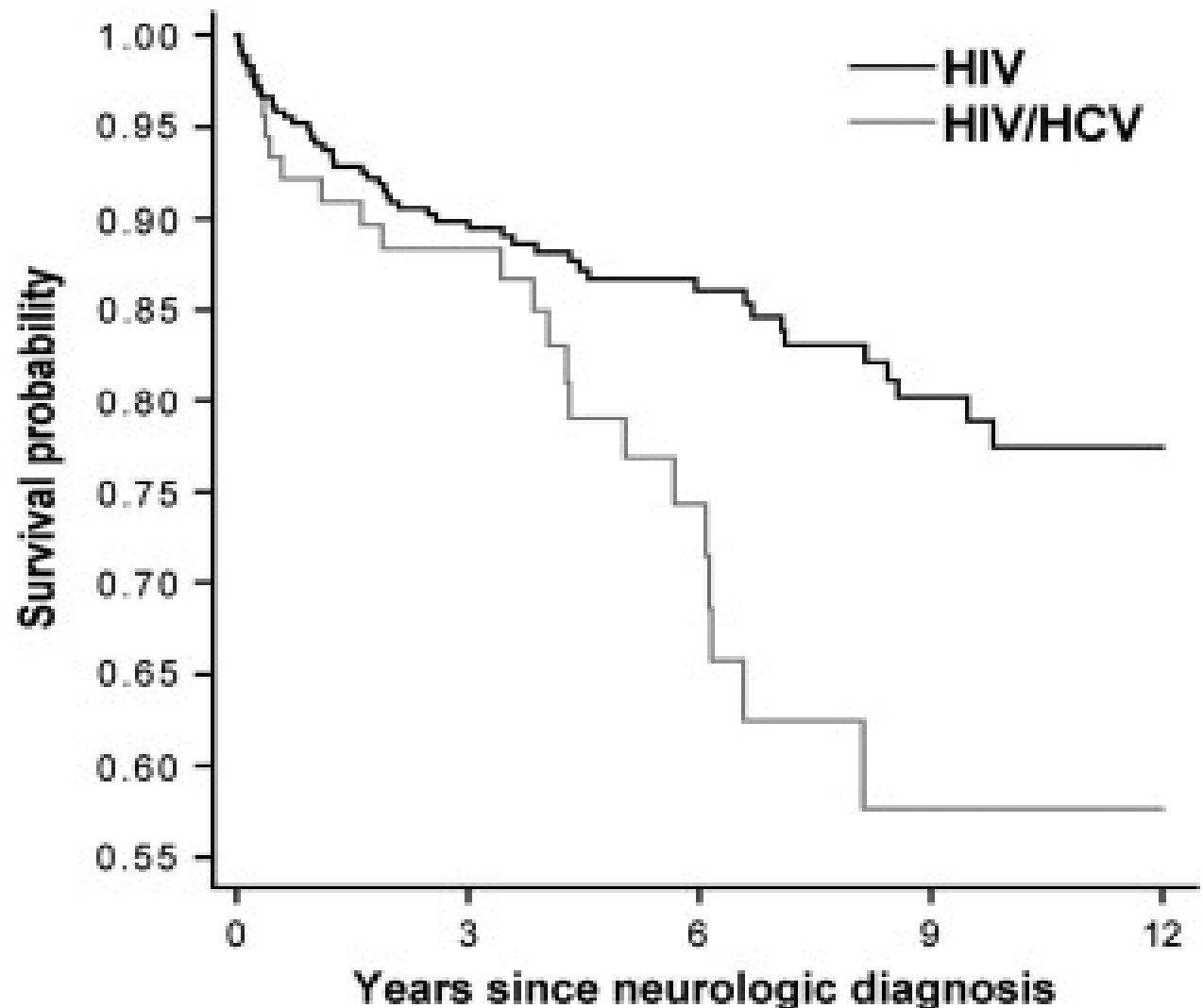


Fracture rates were significantly higher among HIV/HCV patients than HIV-only patients (2.57 versus 2.07/1000 patient-years, relative risk = 1.24, $p < 0.0001$).



Hepatitis C virus co-infection increases neurocognitive impairment severity and risk of death in treated HIV/AIDS

The presence of HCV co-infection among HIV-infected individuals increased neurologic disease burden and risk of death, underscoring HCV's capacity to affect the nervous system and survival of HIV-infected persons.





Insulin resistance is associated with progression to hepatic fibrosis in a cohort of HIV/hepatitis C virus-coinfected patients

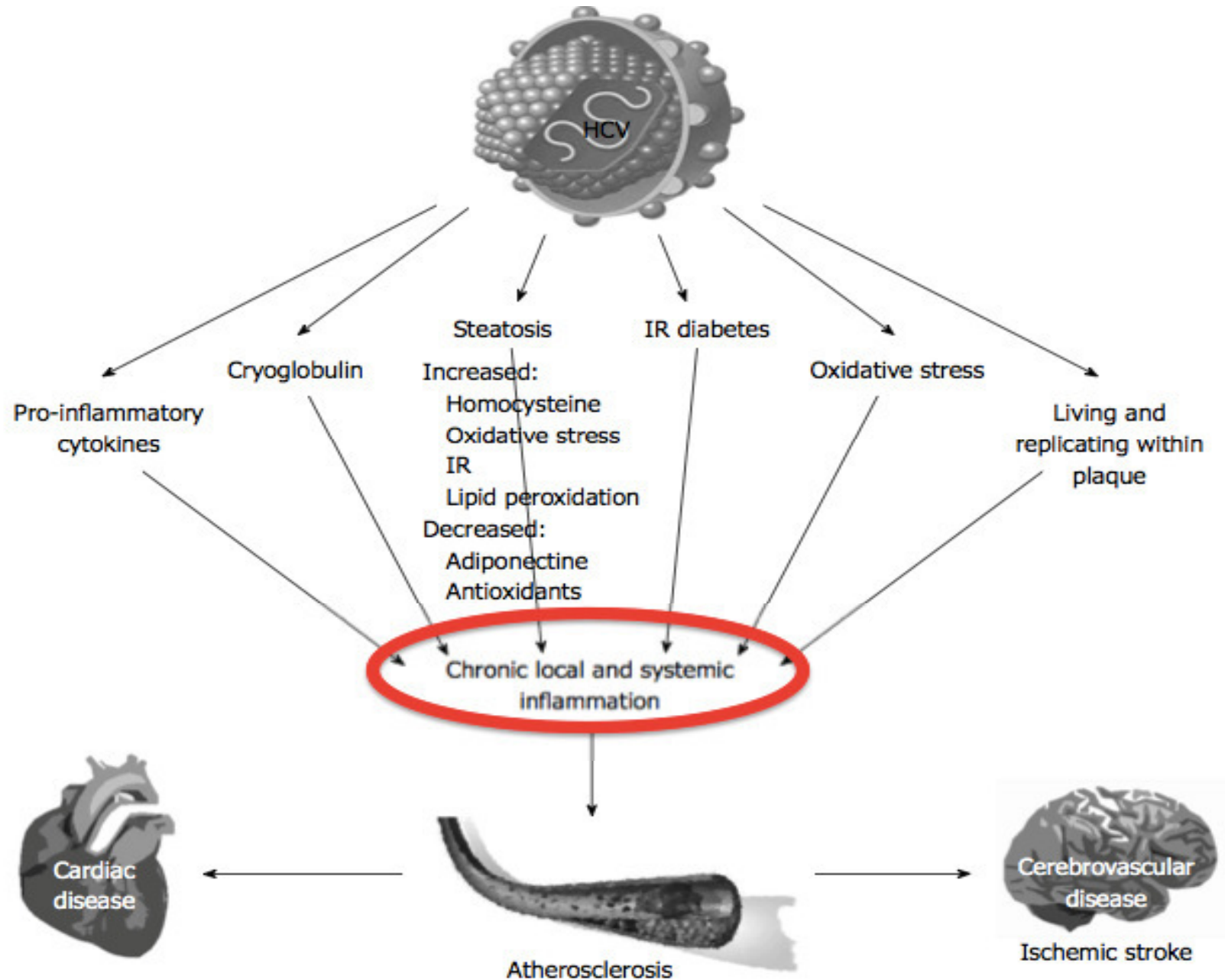
Table 2. Multivariate Cox proportional hazards model of factors associated with development of aspartate aminotransferase-to-platelet ratio index score of at least 1.5 during follow-up.

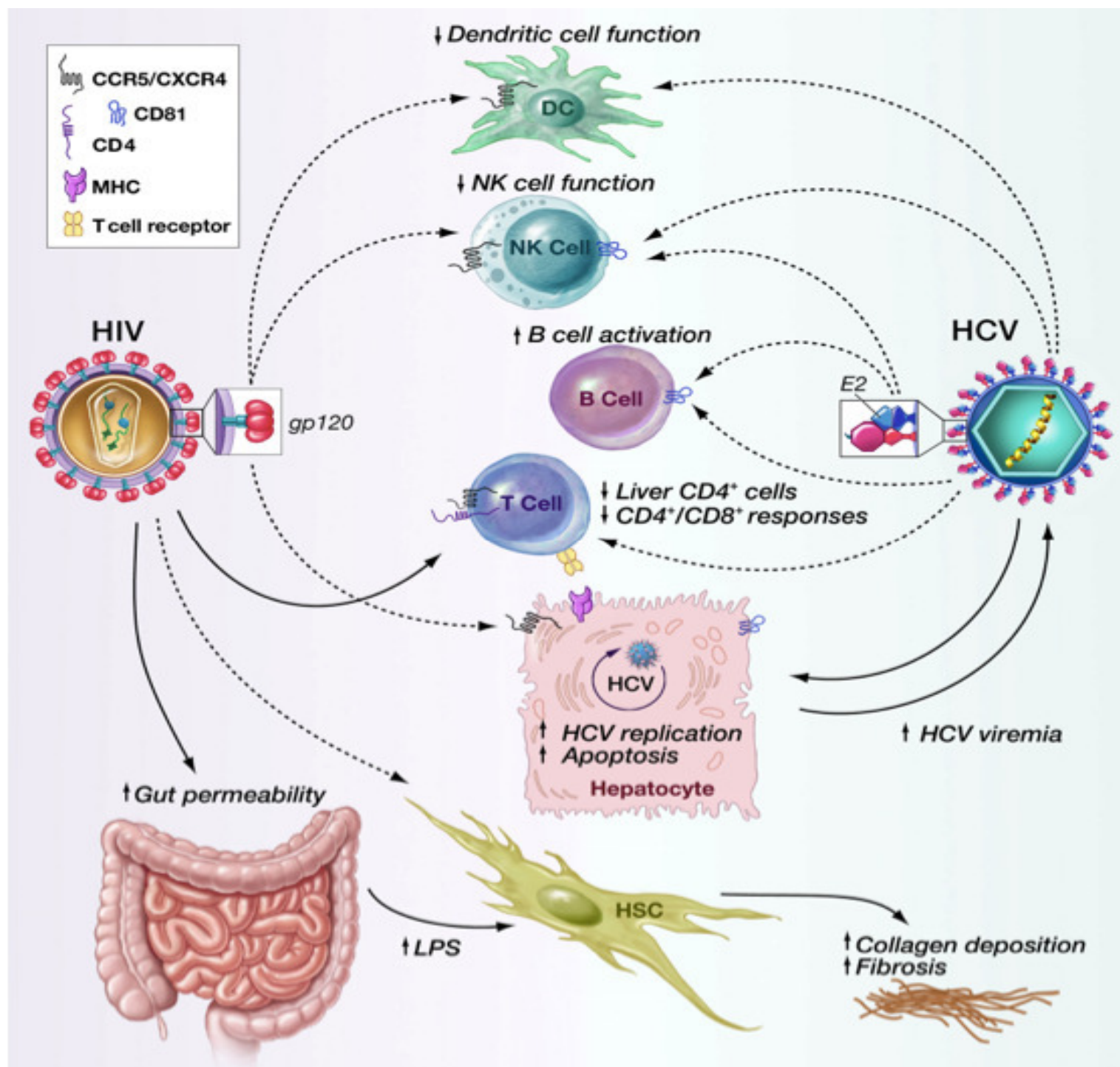
Variables	Adjusted hazard ratio	95% confidence interval
Insulin resistance modelled as HOMA-IR ≥ 2 vs. < 2		
HOMA-IR > 2	7.72	2.55–23.36
Age (years)	0.98	0.88–1.09
Female sex	0.85	0.27–2.63
Duration of HCV infection (per year)	1.05	0.99–1.12
BMI ≥ 25	0.73	0.24–2.28
Baseline APRI (ln)	7.92	1.94–32.42
Time updated CD4 cell count (per 100 cells/ μ l)	0.92	0.81–1.06
Time updated HIV viral load < 50 copies/ml	0.74	0.24–2.29
Insulin resistance modelled with HOMA-IR as a continuous variable		
HOMA-IR (log-base 2)	1.48	1.12–1.86
Age (years)	1.00	0.91–1.09
Female sex	0.82	0.26–2.55
Duration of HCV infection (per year)	1.02	0.97–1.10
BMI ≥ 25	0.83	0.29–2.34
Baseline APRI (ln)	5.20	1.31–20.69
Time updated CD4 cell count (per 100 cells/ μ l)	0.92	0.79–1.08
Time updated HIV viral load < 50 copies/ml	0.77	0.20–2.99

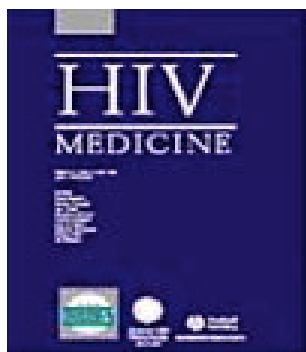
The population ($n = 85$) is defined as those with no baseline history of fibrosis or end-stage liver disease and confirmed presence of hepatitis C virus (HCV)-RNA. Median follow-up period was 1.4 years (interquartile range 1.0, 1.7 years). APRI, aspartate aminotransferase-to-platelet ratio index; HOMA-IR, homeostasis model for assessment of insulin resistance.

Conclusion: In this first longitudinal analysis, insulin resistance was very common among coinfectd patients and was associated with modifiable risk factors such as elevated BMI. Insulin resistance was found to be strongly associated with progression to hepatic fibrosis over time.

Pathogeneic mechanisms associated with the development of inflammation in chronic HCV infection

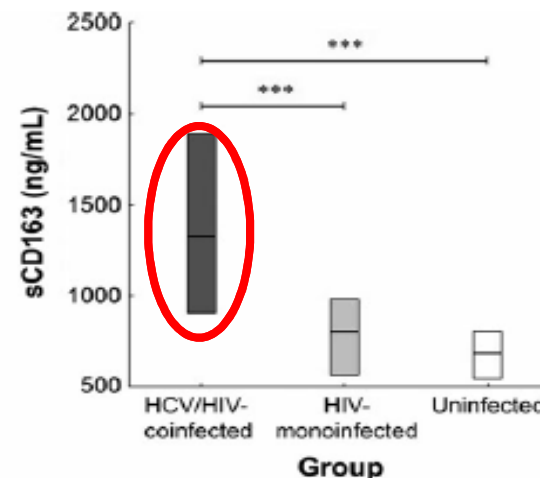
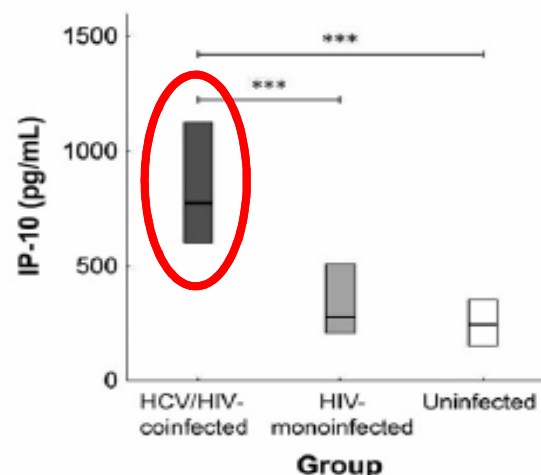
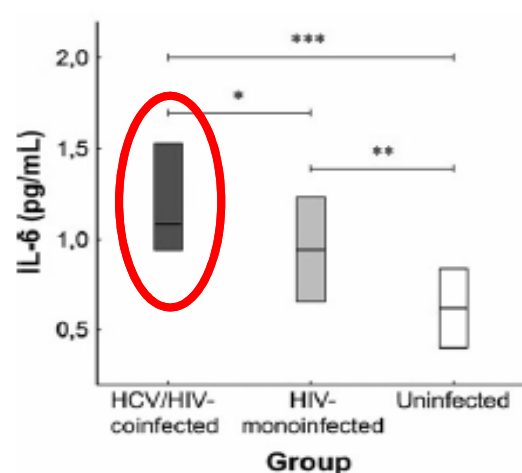




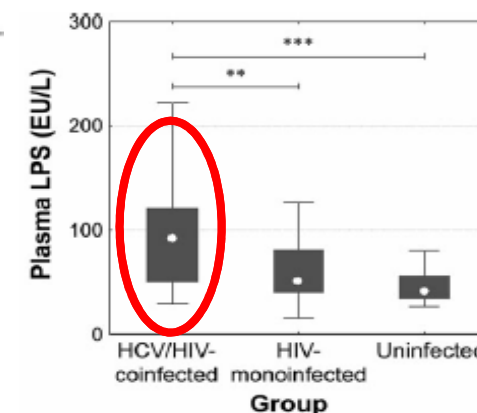
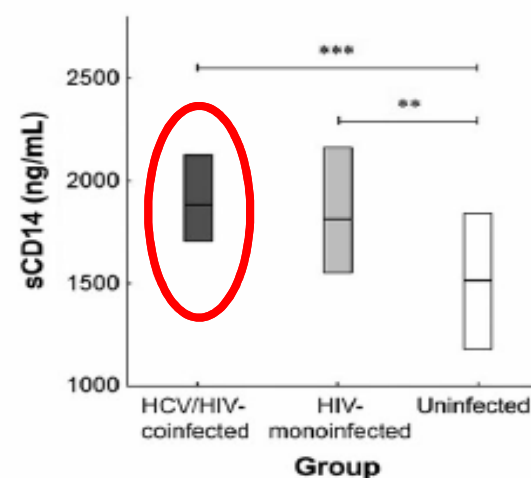
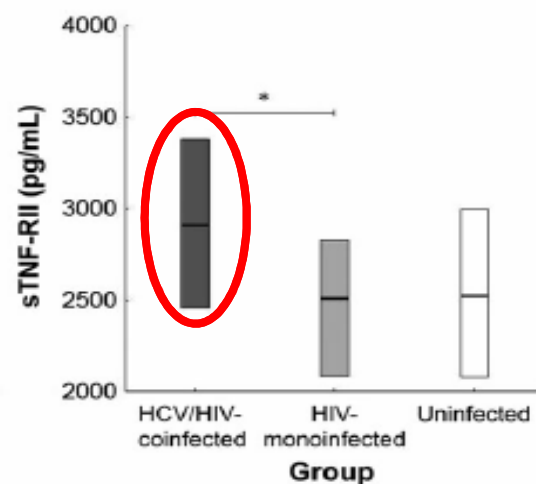
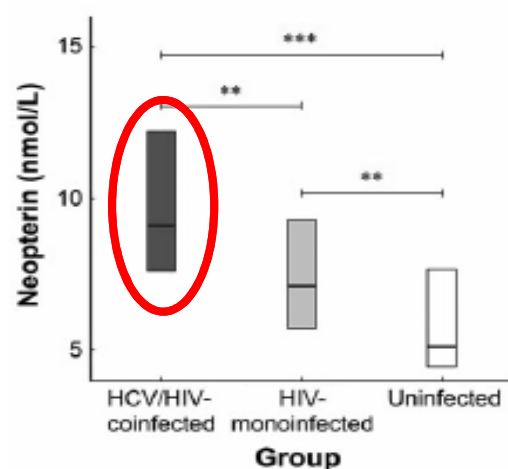


Systemic inflammation and liver damage in HIV/hepatitis C virus coinfection

70 HIV patients on ART (2years), VL<50



*P < 0.05;
**P < 0.01;
***P < 0.001





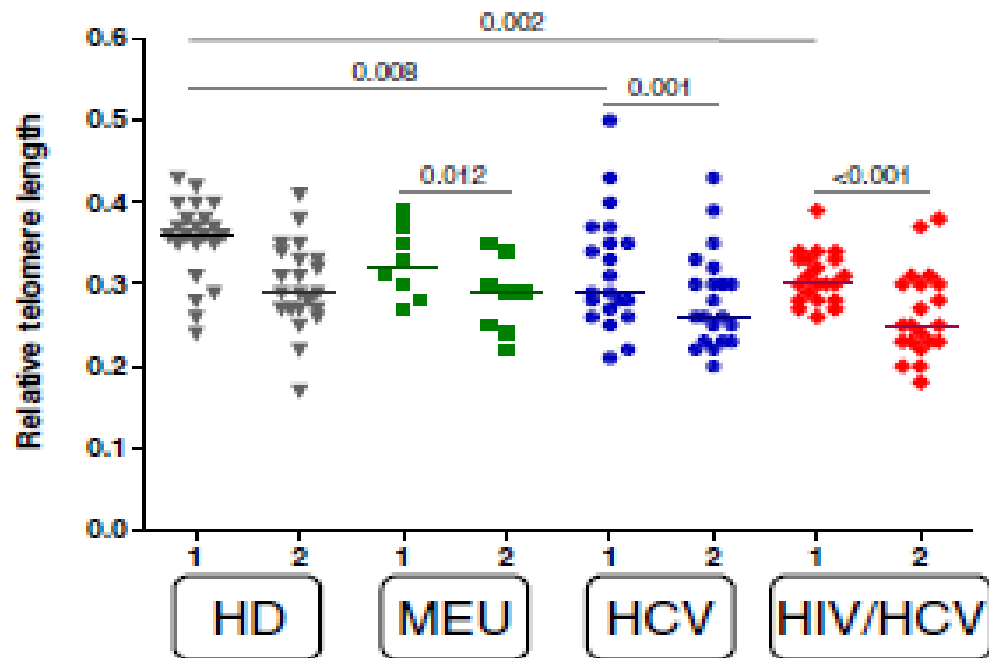
HCV monoinfection and HIV/HCV coinfection enhance T-cell immune senescence in injecting drug users early during infection

BP Grady. Immunity & Ageing 2016

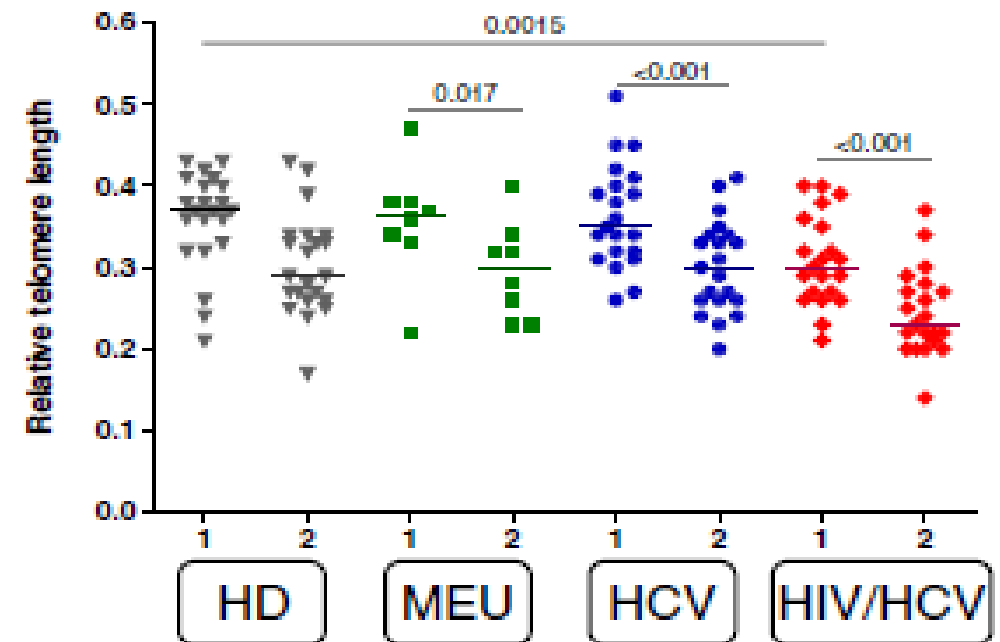
Telomeres are repetitive in nucleotide sequences that shorten with each cell division. > 60 years, short leukocyte telomere length has been associated with higher mortality rates from infectious diseases

A

CD4 cells



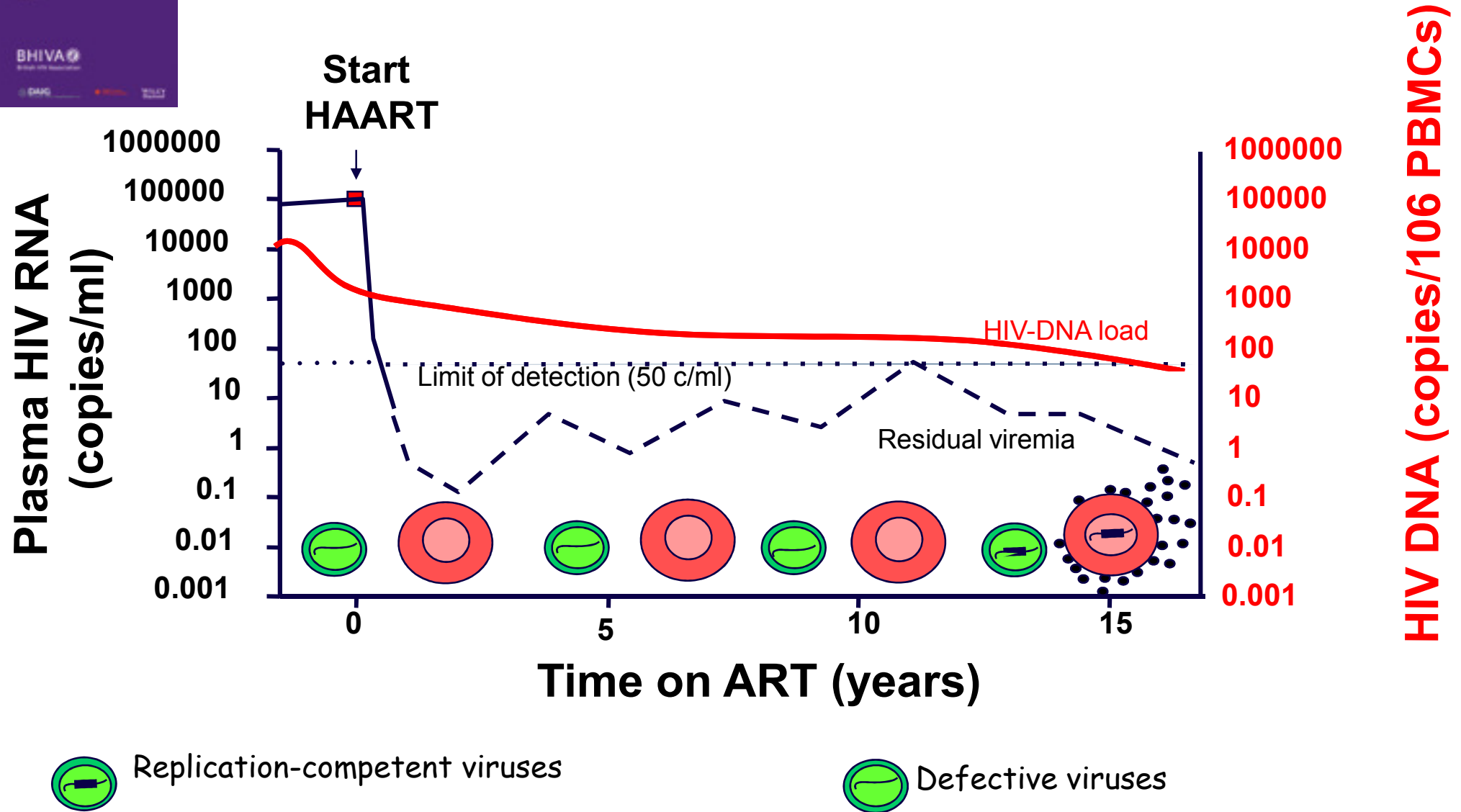
CD8 cells



23 HIV/HCV coinfectd, 21 HCV infected, and 8 MEU (multiple exposed uninfected) and HD (healty donor).



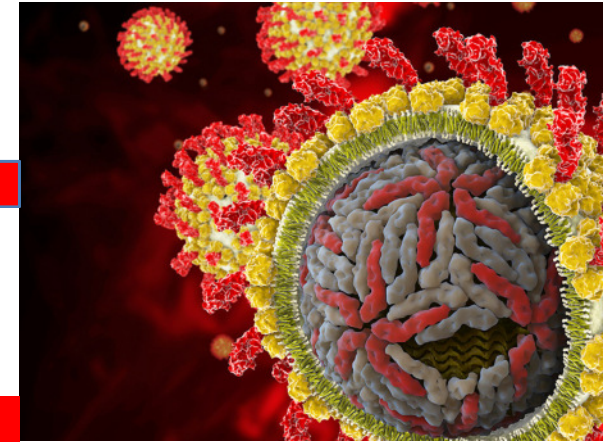
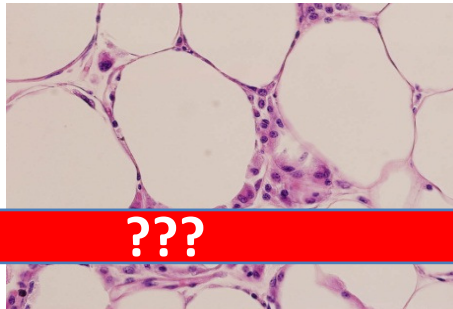
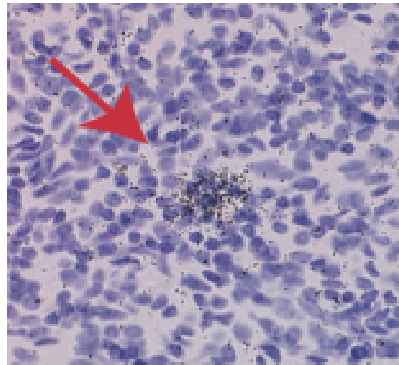
Long lived cells containing non-defective HIV are a very small fraction of total DNA positive-cells (<1%)



**HIV-associated fat
Metabolic syndrome**

HCV Excess pathogens

**HIV production
HIV replication**

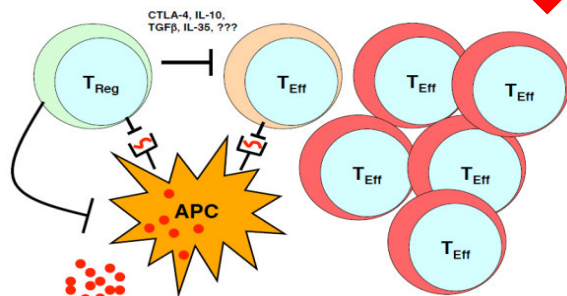


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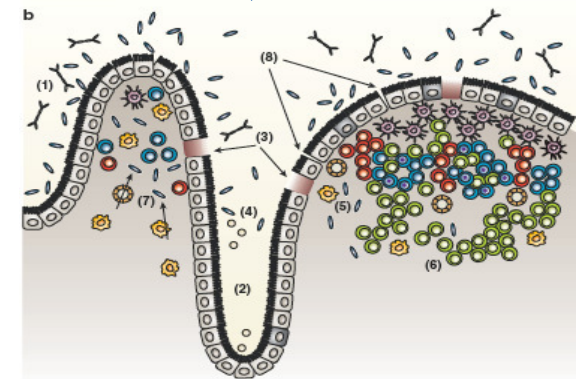
Inflammation

↑ Endothelium adhesion
↑ Monocyte activation
Dyslipidemia
Hypercoagulation/
thrombotic events
Endothelial dysfunction

**Increased incidence of
comorbidities and
clinical disease**



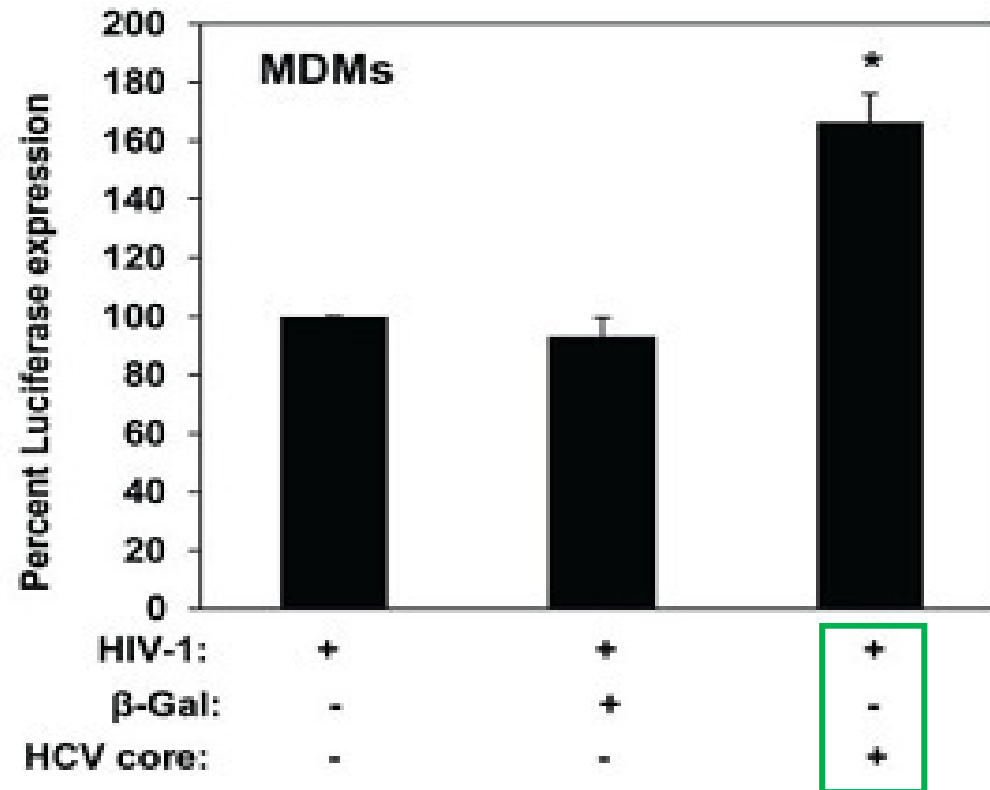
**HIV-mediated loss of
regulatory cells (Tregs)**



**Microbial
translocation**



HCV core protein enhances HIV-1 replication in human macrophages

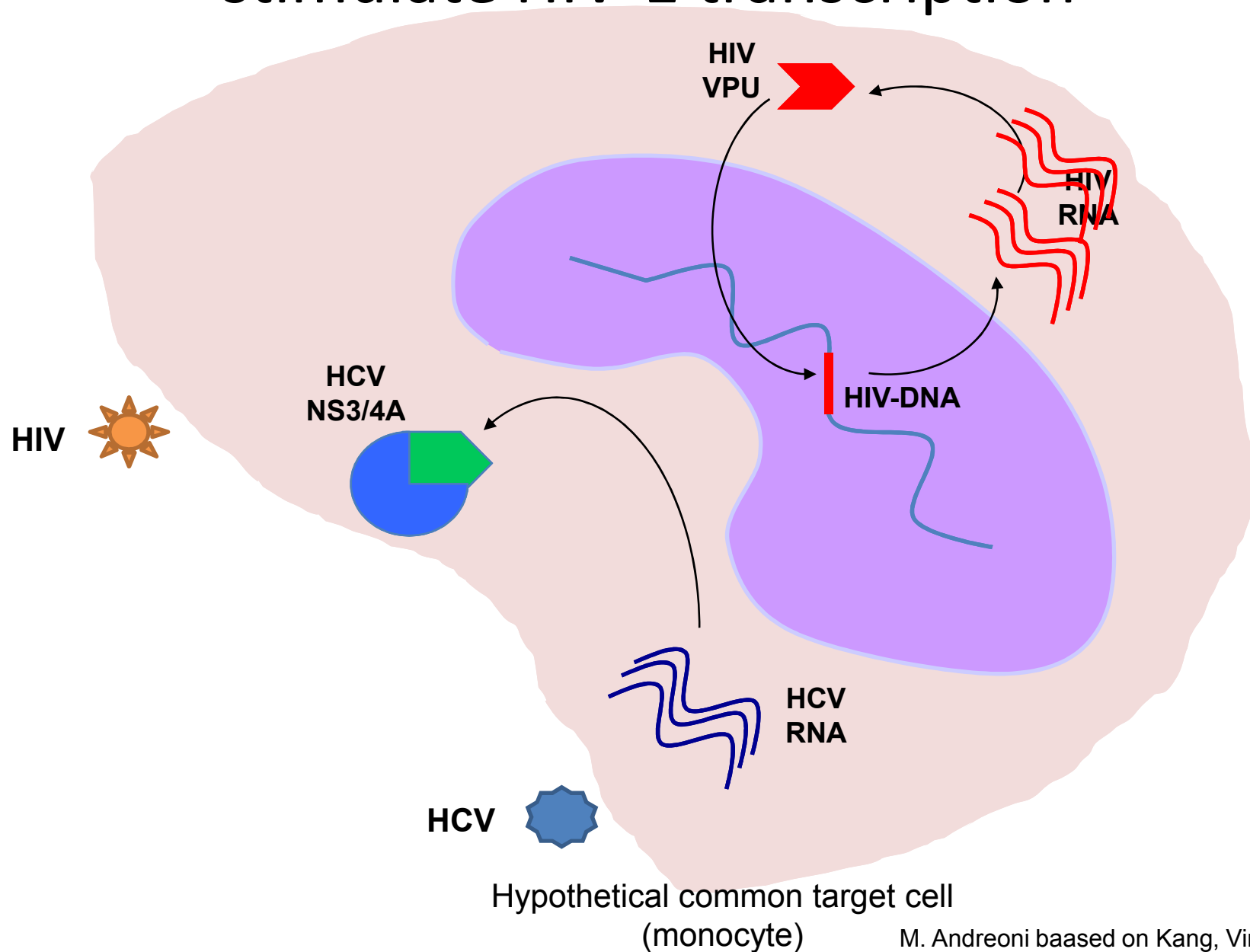


HCV core enhances HIV-1 infection of human monocyte derived macrophages

Primary human macrophages (MDMs) were stimulated with 5 µg/ml of HCV core, or β-Gal recombinant protein control at 12 hours after HIV-1 BaL infection. LTR-driven Luciferase activity was measured 2 days after infection.

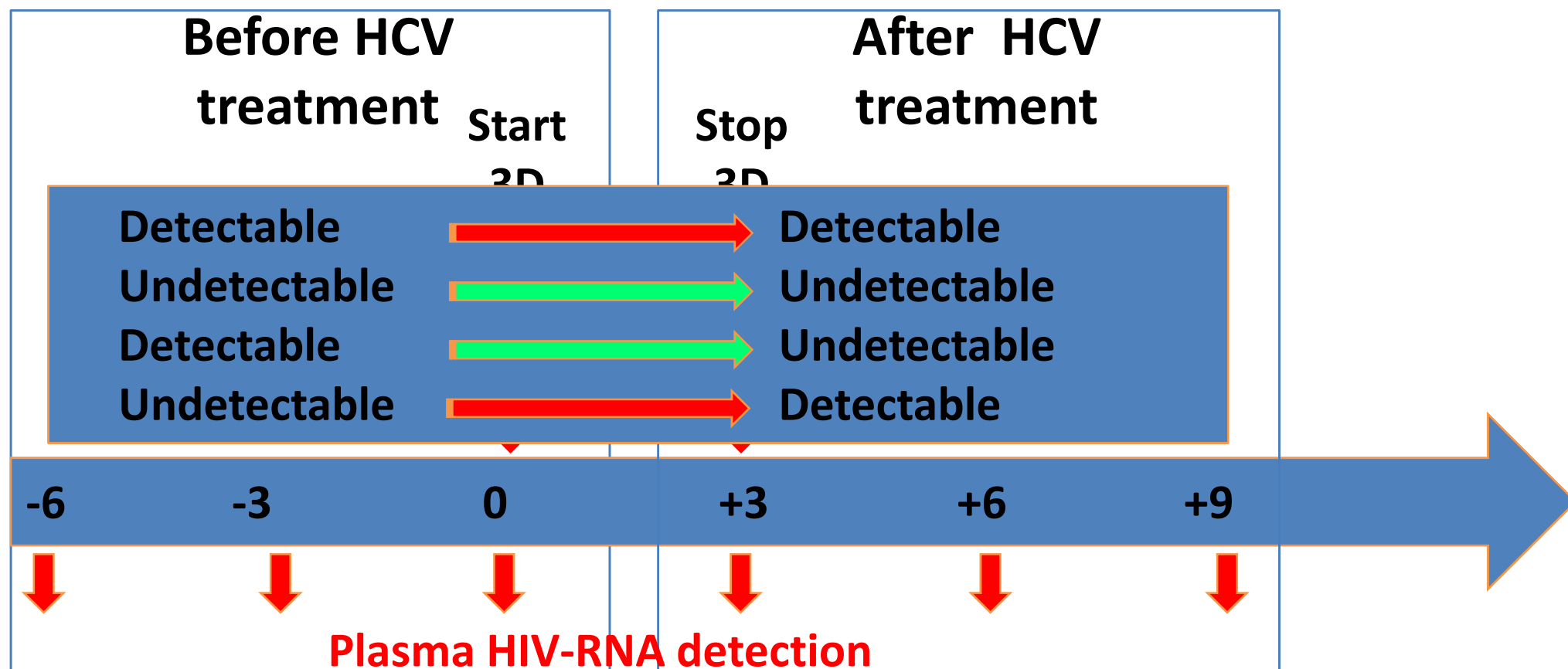


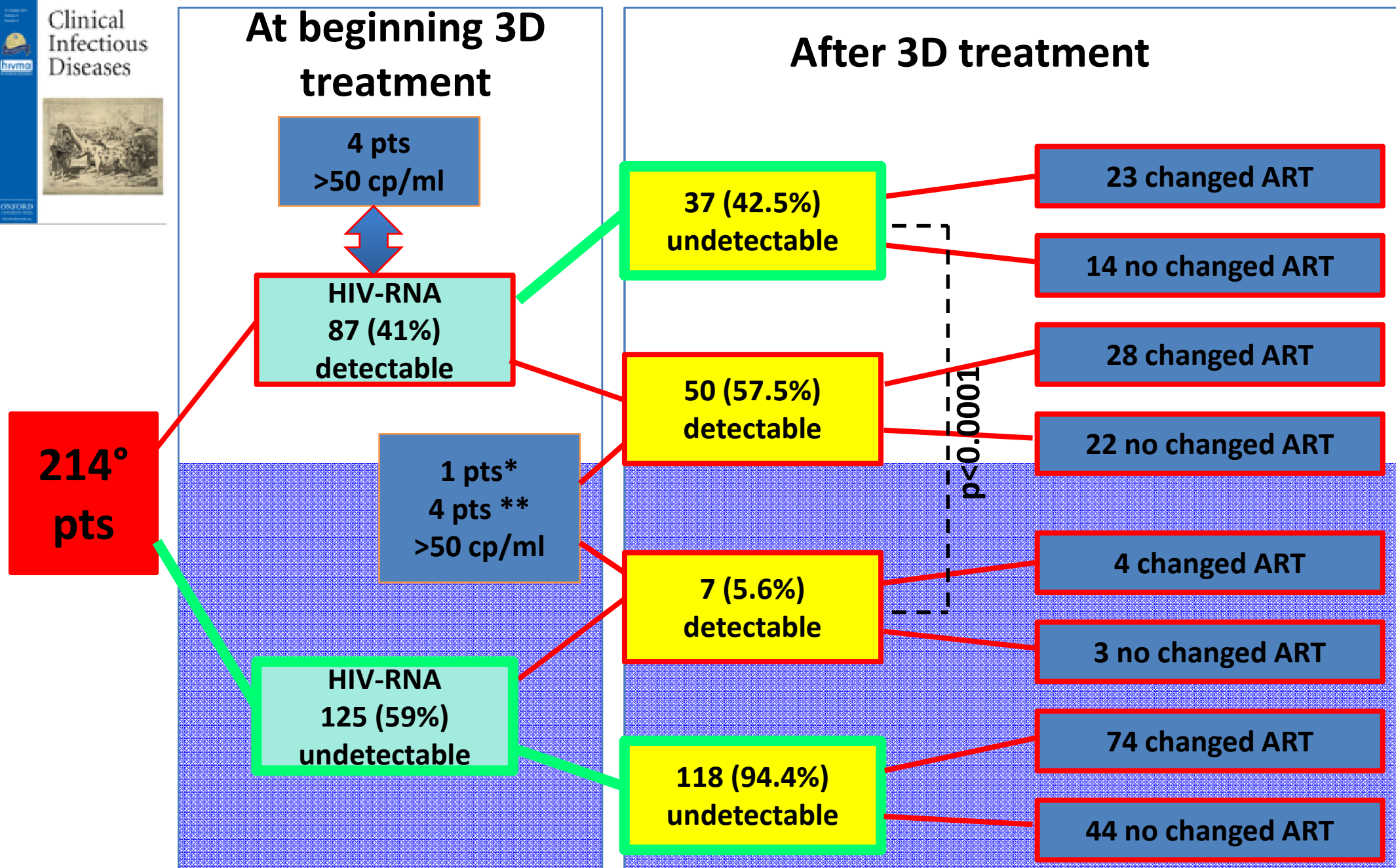
HCV NS3/4A interacts with HIV-1 Vpu to stimulate HIV-1 transcription



Classification of patients according to the presence or not of residual plasma viremia

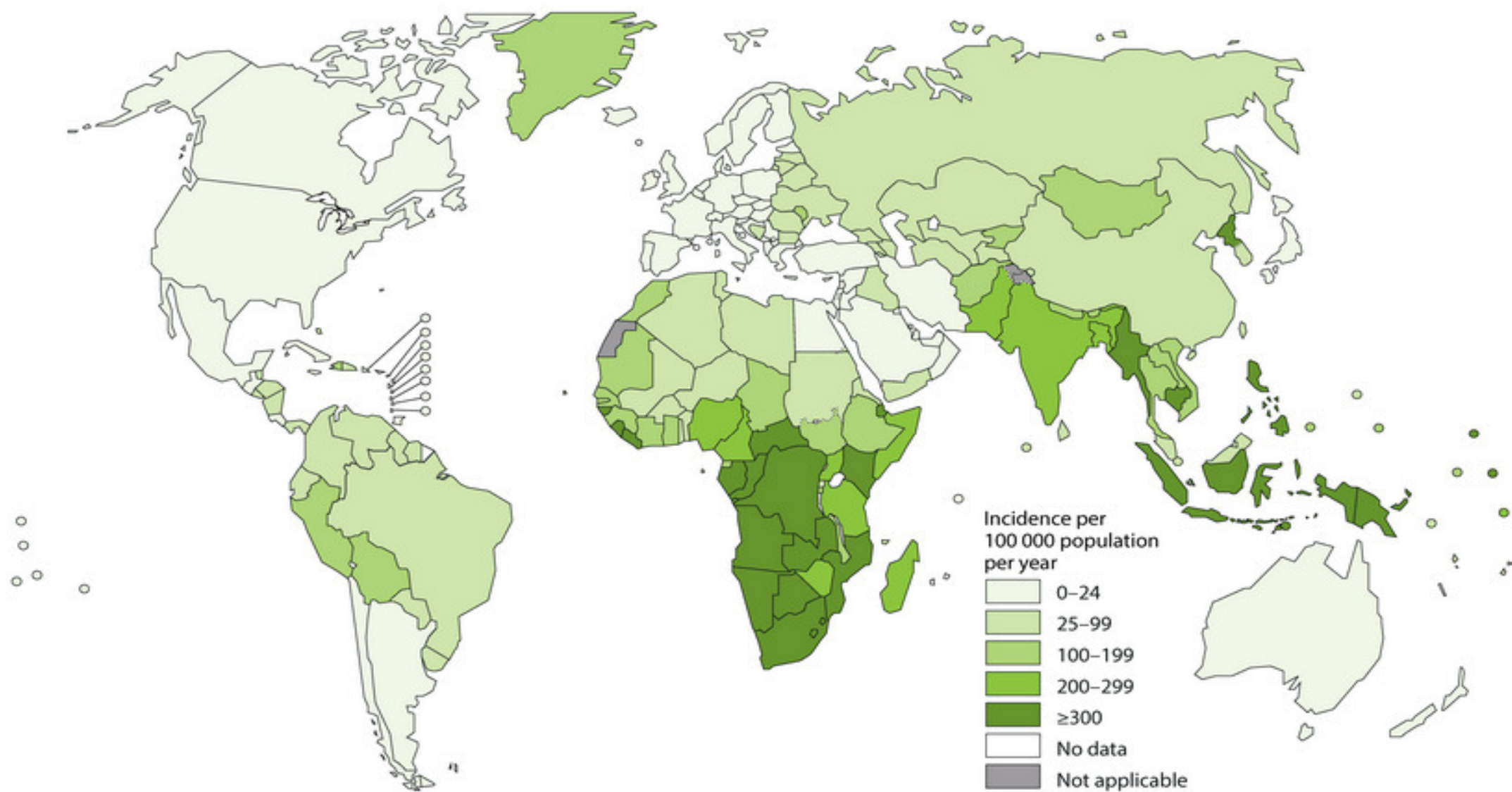
Patient was classified to have a residual plasma viremia if had HIV-RNA detected in at least one occasion on the three evaluations before or after start 3D





*change therapy and **3 change therapy ° 2 pts lost follow-up

Estimated TB incidence rates, 2016



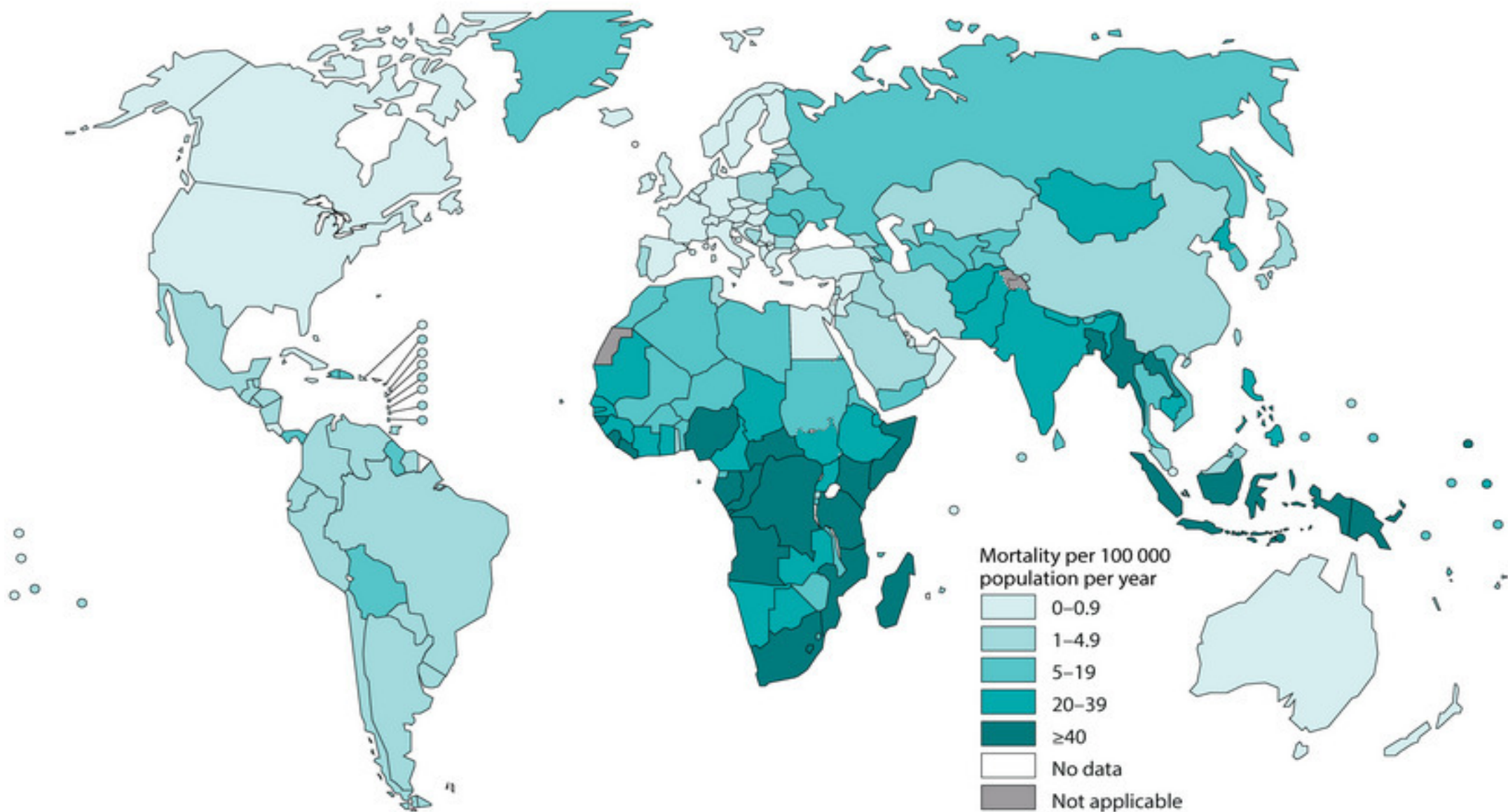
Data Source: *Global Tuberculosis Report 2017*. WHO, 2017.

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World Health Organization

Estimated TB mortality rates excluding TB deaths among HIV-positive people, 2016



Data Source: *Global Tuberculosis Report 2017*. WHO, 2017.

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World Health
Organization

Epidemiologia italiana

Population 2016

59 million

Estimates of TB burden*, 2016	Number (thousands)	Rate (per 100 000 population)
Mortality (excludes HIV+TB)	0.33 (0.33–0.34)	0.56 (0.56–0.57)
Mortality (HIV+TB only)	0.063 (0.032–0.11)	0.11 (0.05–0.18)
Incidence (includes HIV+TB)	3.7 (3.1–4.2)	6.1 (5.3–7.1)
Incidence (HIV+TB only)	0.41 (0.24–0.63)	0.69 (0.4–1.1)
Incidence (MDR/RR-TB)**	0.14 (0.095–0.19)	0.24 (0.16–0.32)

Estimated TB incidence by age and sex (thousands)*, 2016			
	0–14 years	> 14 years	Total
Females	0.14 (0.12–0.16)	1.2 (0.99–1.3)	1.3 (1.1–1.5)
Males	0.16 (0.13–0.18)	2.2 (1.9–2.5)	2.3 (2–2.7)
Total	0.3 (0.25–0.34)	3.4 (2.8–3.9)	3.7 (3.1–4.2)

TB case notifications, 2016	
Total cases notified	4 032
Total new and relapse	3 778
- % tested with rapid diagnostics at time of diagnosis	0%
- % with known HIV status	
- % pulmonary	69%
- % bacteriologically confirmed among pulmonary	91%

TB disease risk is high among PWID

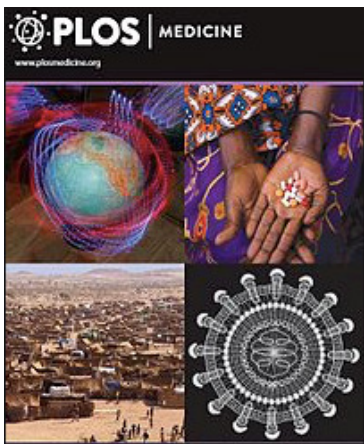
Risk Group	%	OR	95%CI	Adjusted OR	95% CI
MSM	18.2	1			
IDU	40.8	3.10	2.6-3.8	2.58	2.1-3.2
Heterosexual	26.5	1.63	1.3-2.1	1.96	1.5-2.6
Unknown	17.7	0.97	0.6-1.6	1.01	0.6-1.7

Factors associated with tuberculosis as an AIDS-defining disease (Barcelona 1994-2005) Source:

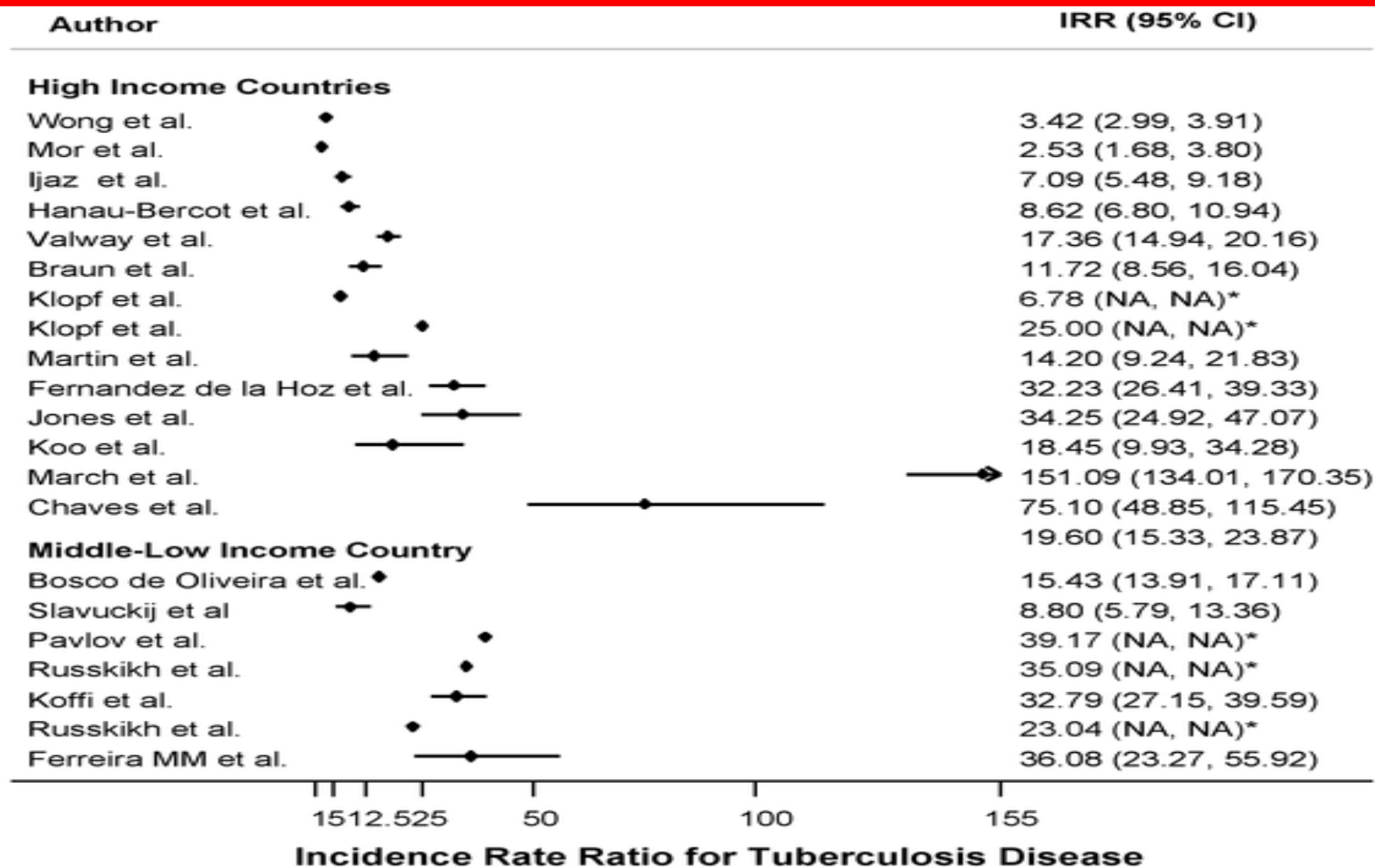
HIV, HBV and HCV common among TB patients

Prevalence of HIV, HBV and HCV among 205 patients with TB in Buenos Aires, Argentina, 2001

Organism	No. positive/ no. studied	% Prevalence (95% CI)
HBV	37/187	19.8 (14.3-26.2)
HCV	22/187	11.8 (7.5-17.3)
HIV	35/205	17.1 (12.2-23.9)



23 times more risk of TB disease in prisoners than the general population



*reported data were insufficient to calculate confidence intervals

Lower survival of TB patients who inject drugs

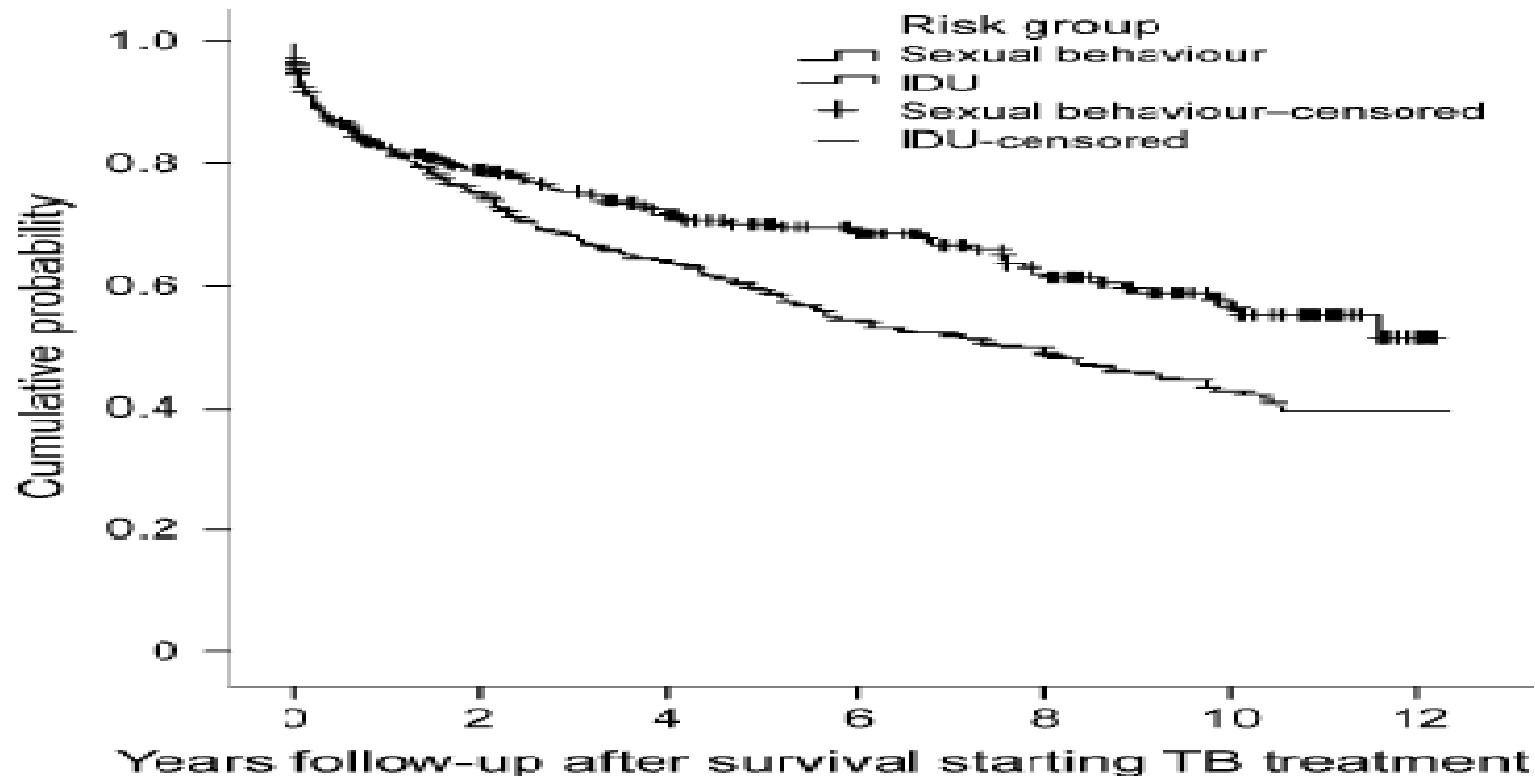
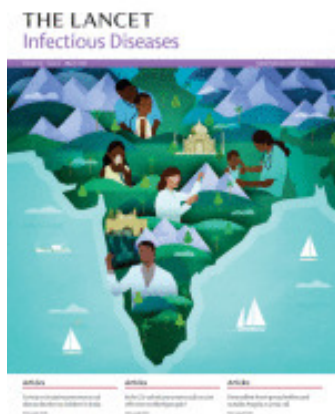


Figure 2 Cumulative survival probability in a cohort of 792 HIV-infected TB patients by category of HIV transmission, Barcelona, 1996–2008. TB = tuberculosis; IDU = injecting drug use; HIV = human immunodeficiency virus. Risk group log rank < 0.001.



ART reduce TB risk by 54-92% among PWID

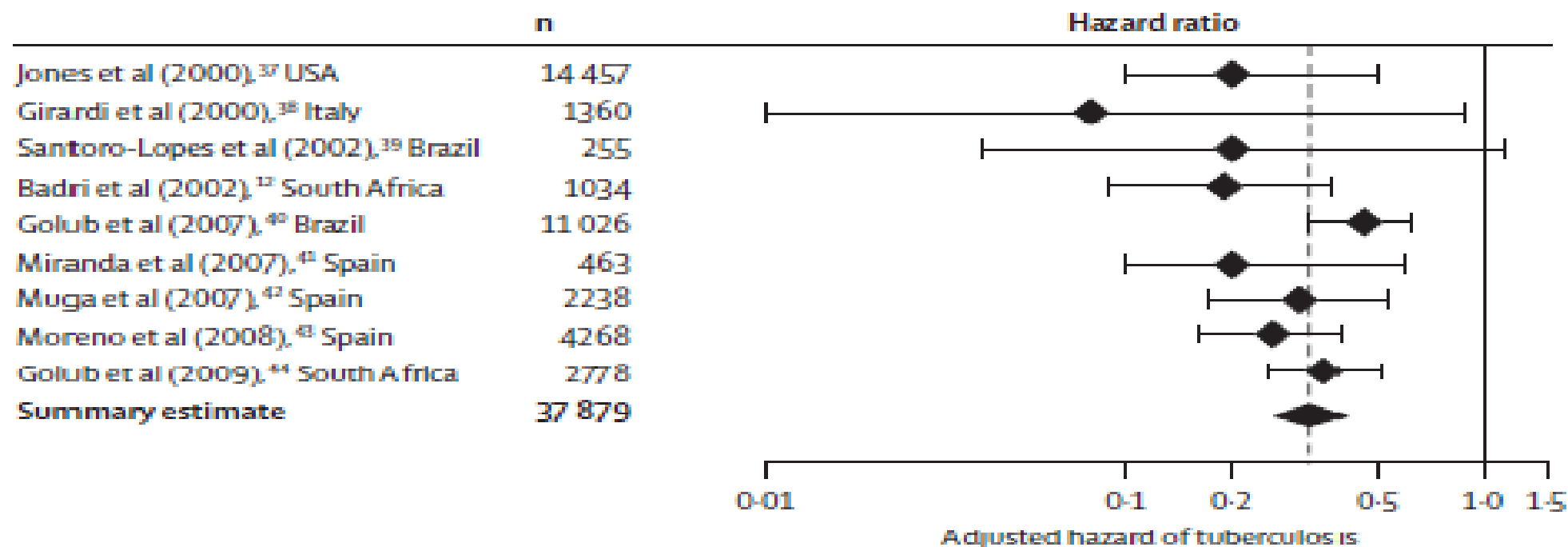
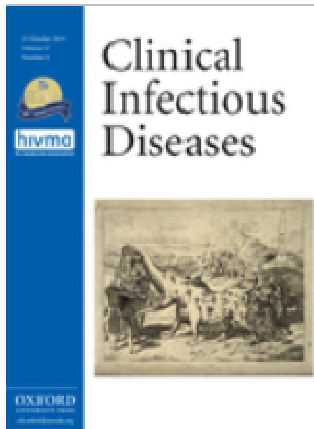


Figure 2: Adjusted hazards of tuberculosis, comparing HIV-infected patients receiving antiretroviral therapy with patients not receiving antiretroviral therapy



Tuberculosis and Drug Use: Review and Update

Robert G. Deiss¹, Timothy C. Rodwell¹, and Richard S. Garfein¹

Drug users, and injection drug users in particular, have driven TB epidemics in a number of countries. The successful identification and treatment of TB among drug users remains an important component of a comprehensive TB strategy, but drug users present a unique set of challenges for TB diagnosis and control.

