Epidemiological, diagnostic and treatment particularities in HIV/HCV co-infected patients

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Workshop HEPCARE EUROPE 30th March 2017

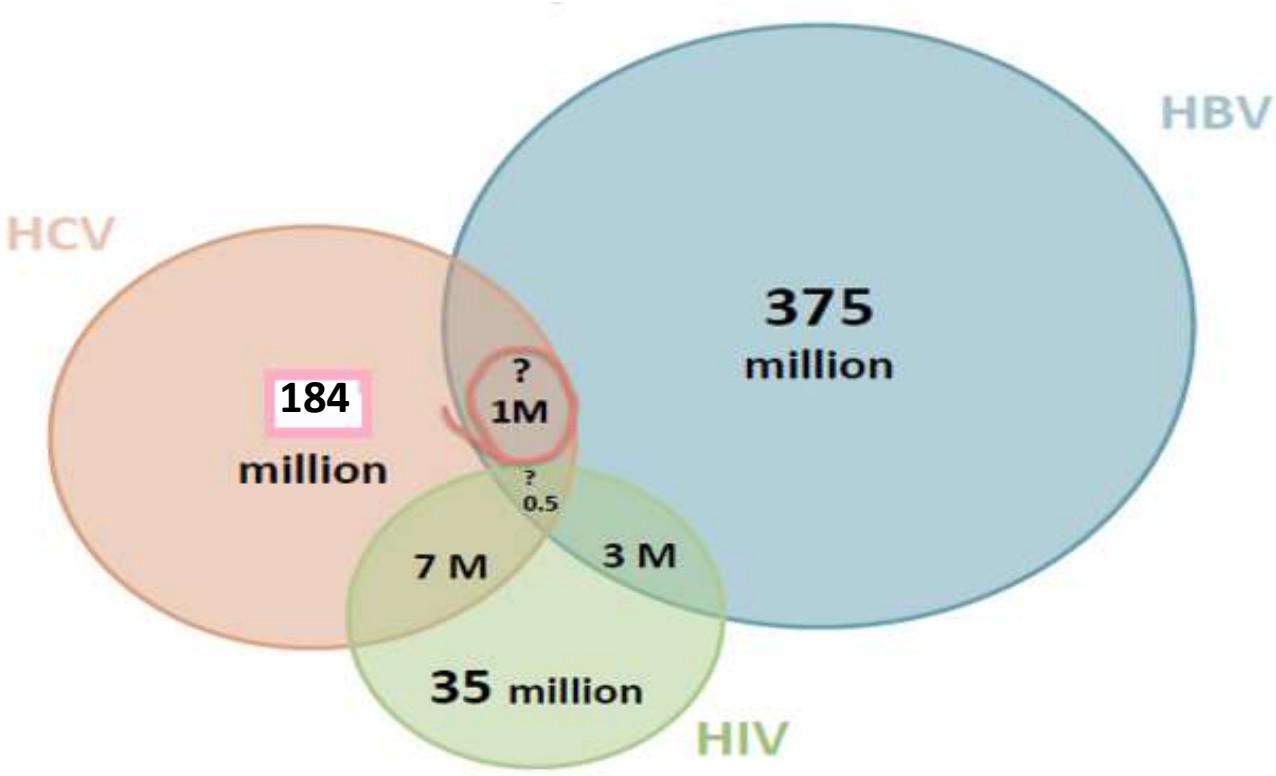
Agenda

- Epidemiology of HIV/HCV
- Diagnostic methods in HIV/HCV co-infected patients
- DAA treatment in HIV/HCV co-infected patients
- Drug - drug interactions in HIV/HCV co-infected patients
- HCV treatment as prevention

Who should be tested for HCV?

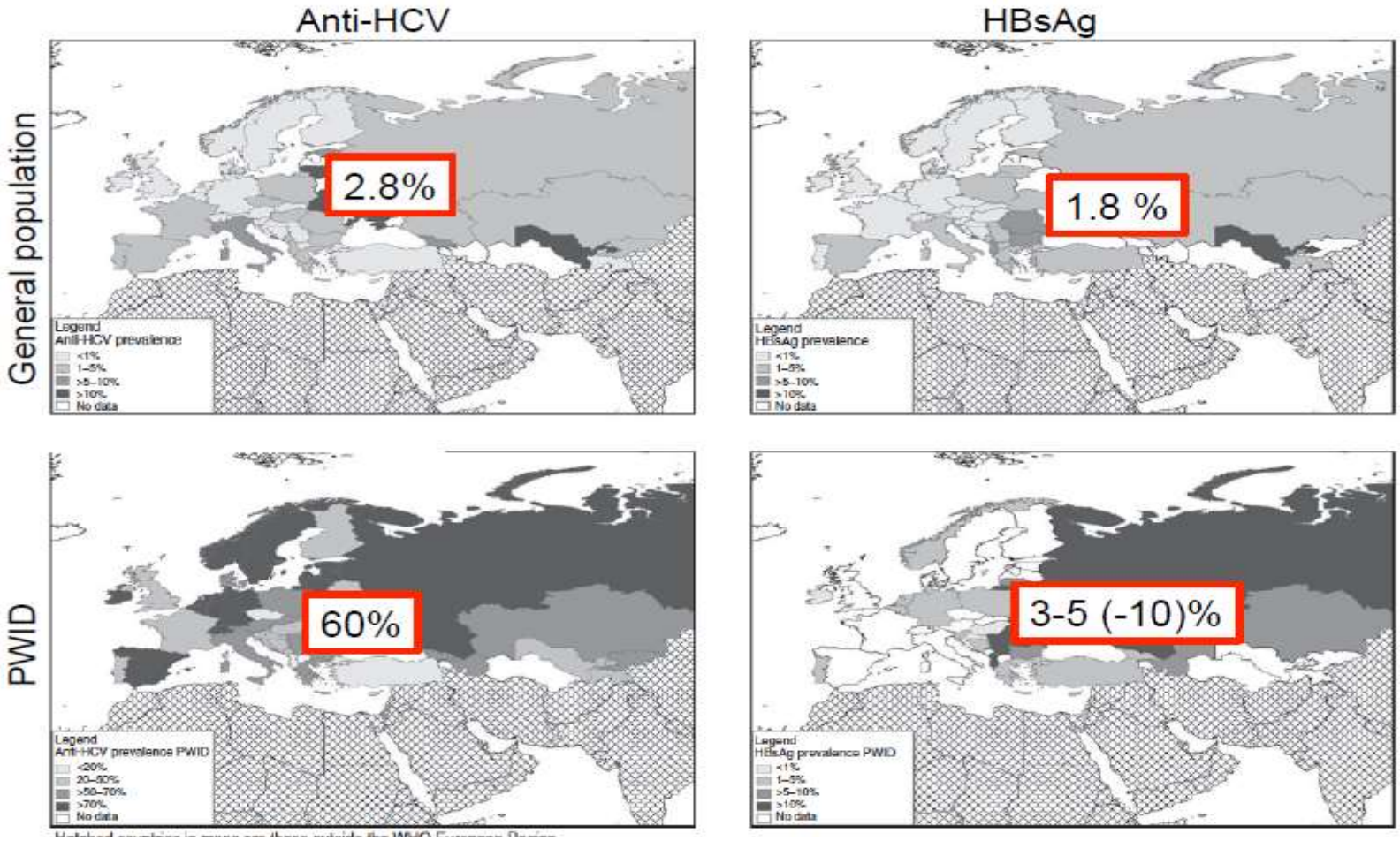
- Intravenous or smoking/snorting drug users
- HIV-infected patients
- Persons with tattoos or piercing, made in unsterile conditions
- Persons born between 1950 - 1990 and/or who received blood transfusions before 1992
- Sexual partners of HCV-infected patients (higher risk in MSM)
- Incarcerated persons or those with history of imprisonment
- Migrants from endemic areas for HCV
- Dialyzed patients
- Persons with history of surgery or invasive procedures (especially before 1992)
- Pregnant women and newborns of HCV-infected mothers
- Persons with increased liver enzymes

Estimated number of HIV/HCV and HIV/HBV co-infected patients

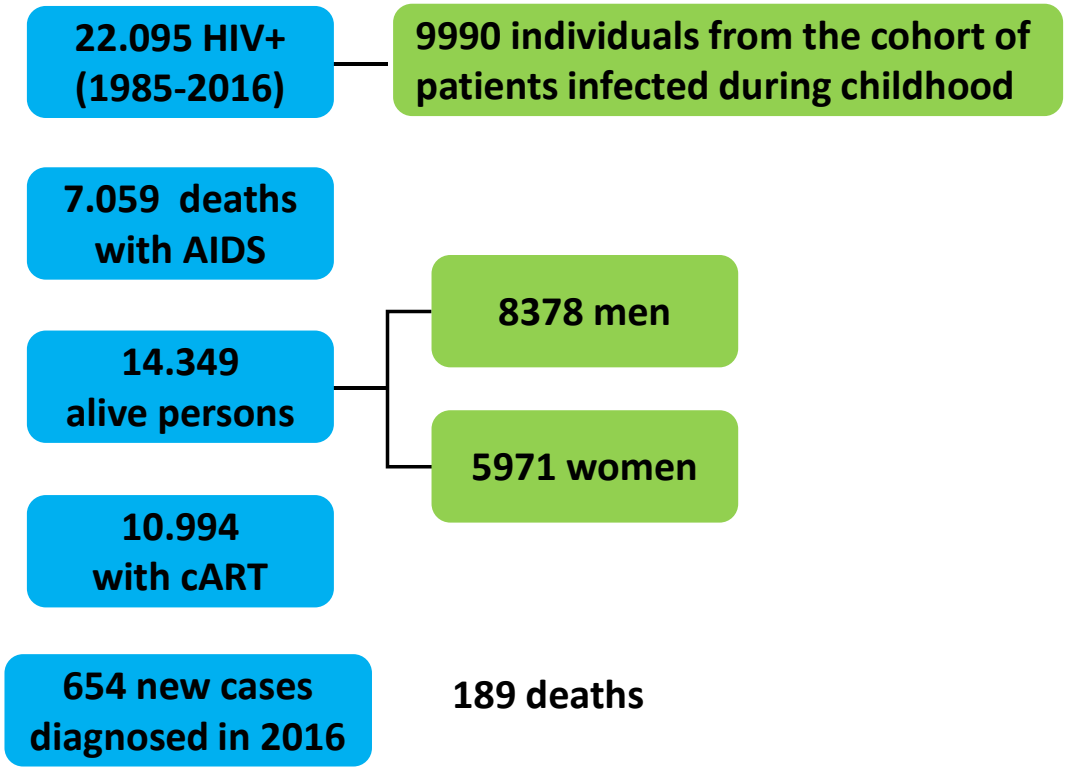


Thrift A et al Nature 2017

Prevalence of HCV and HBV infection in the general population and in people who inject drugs



HIV/AIDS infection in Romania
31th December 2016 (period of time 1985 - 2016)



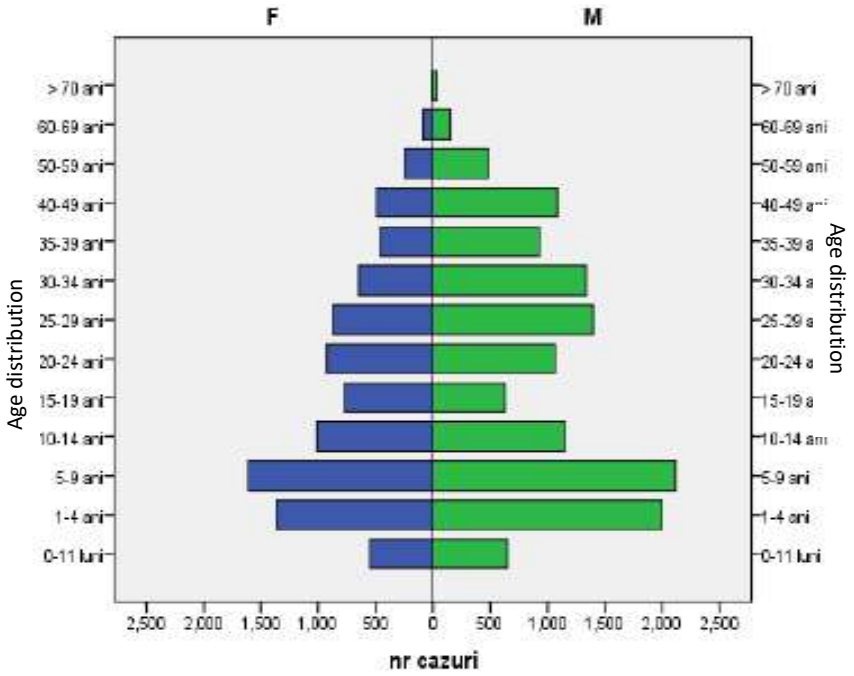
cART combined antiretroviral treatment

Compartment for Monitoring and Evaluation of HIV/AIDS in Romania - "Matei Bals"
National Institute for Infectious Diseases, Romanian Ministry of Health

Pyramid of ages for HIV-infected patients in Romania

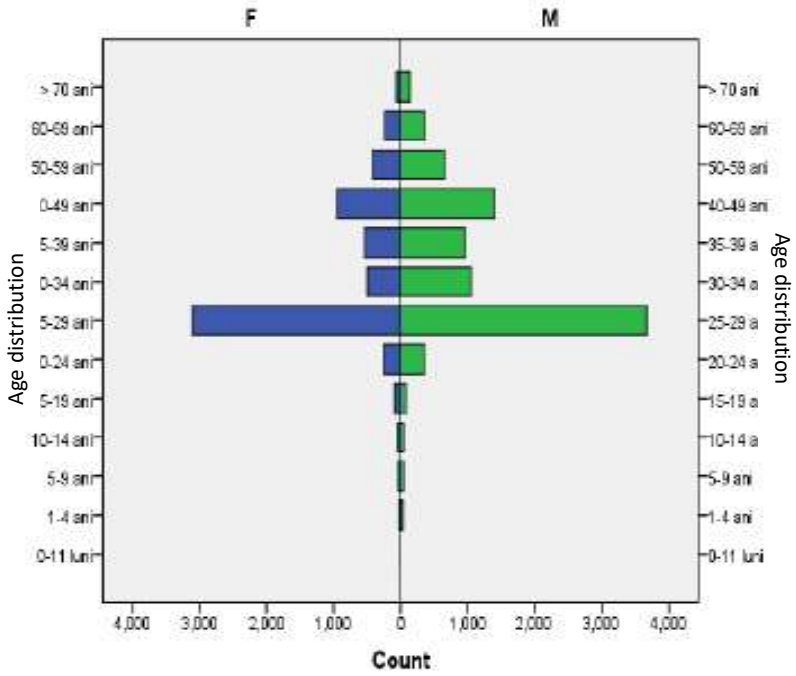
Age at time of diagnosis/notification
Cumulative total 1985-2016

Age distribution at the time of first positive test
Gender



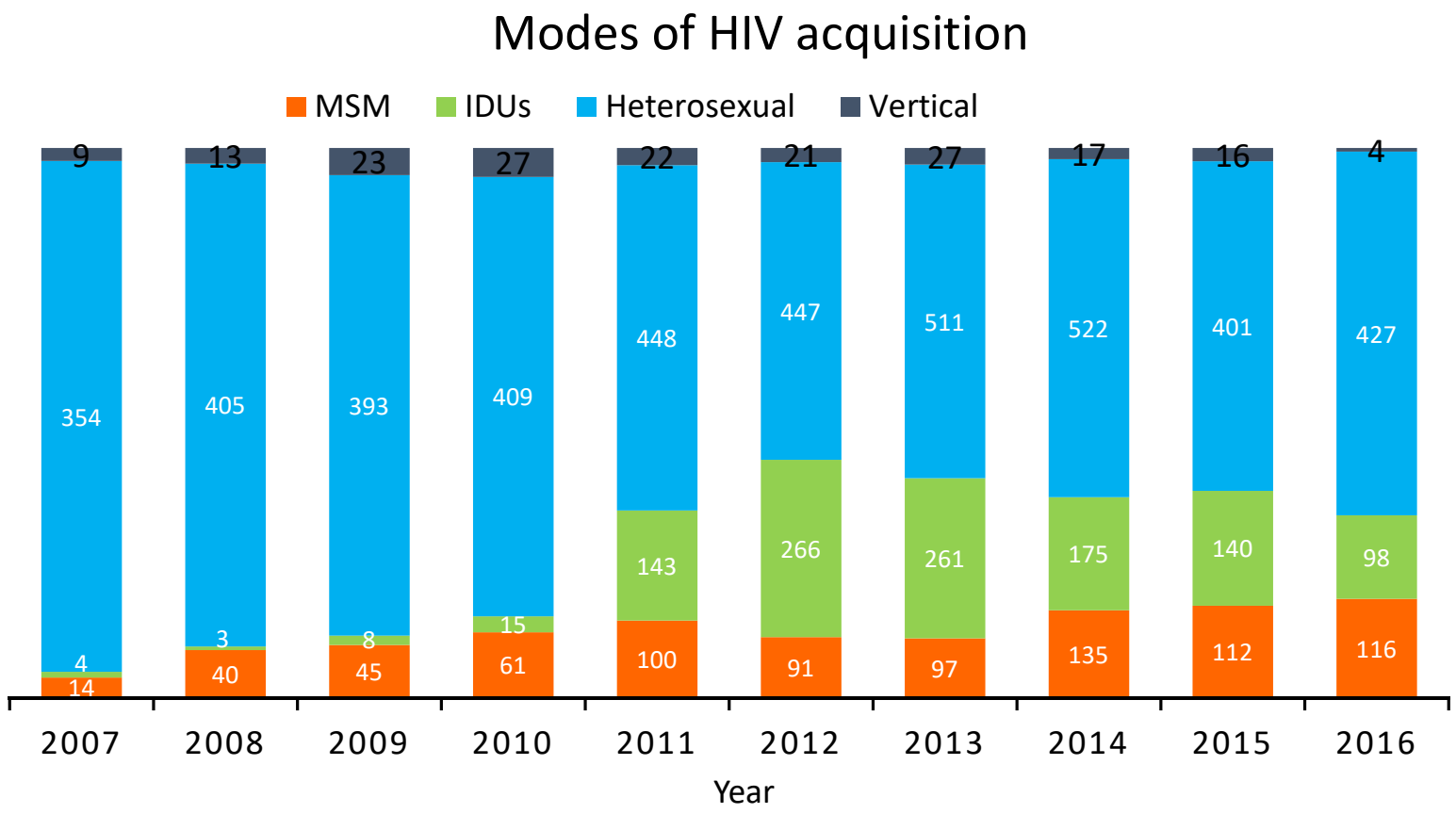
Age distribution of living patients

Age distribution at 31th December 2016
Gender



Compartment for Monitoring and Evaluation of HIV/AIDS in Romania - “Matei Bals” National Institute for Infectious Diseases, Romanian Ministry of Health

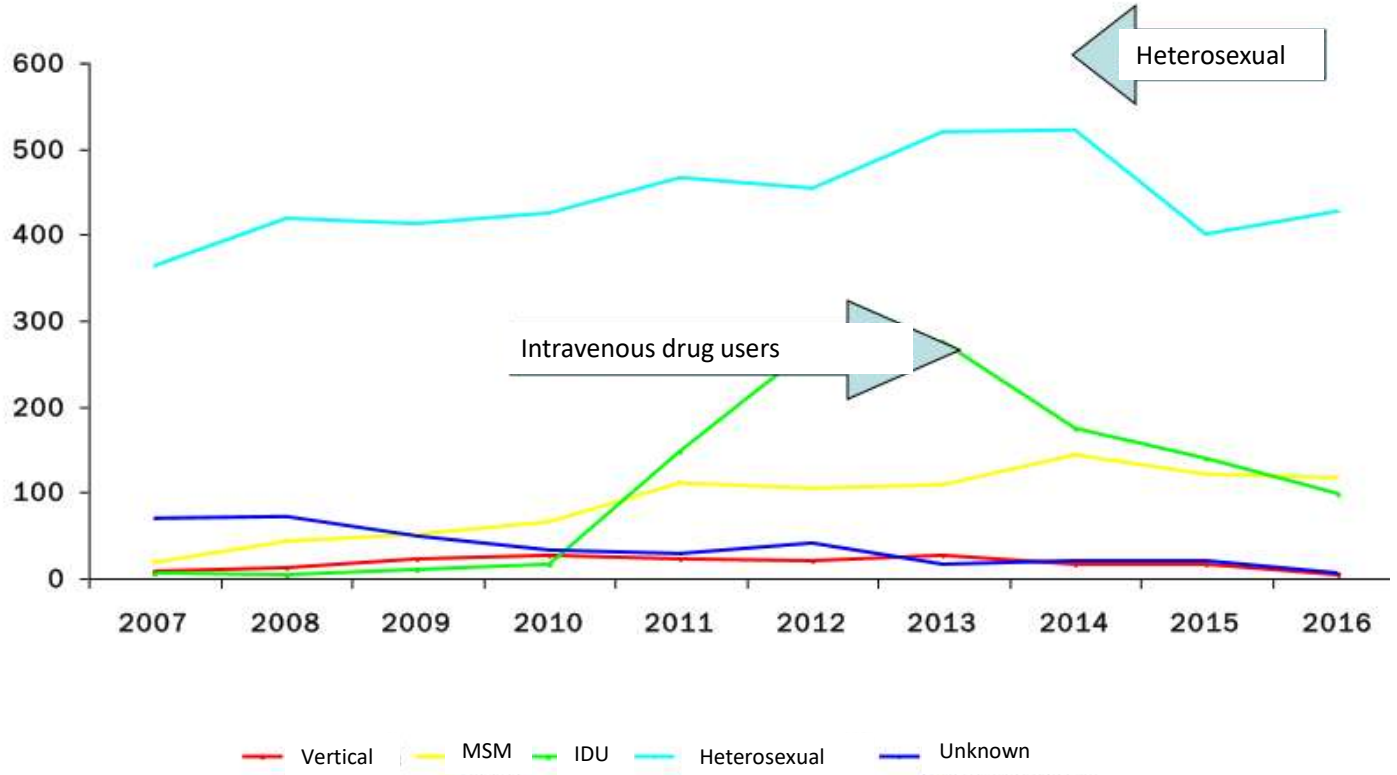
Dynamics of the HIV epidemic in Romania (2007 - 2016)



IDU, injection drug users; MSM, men who have sex with men

CNLAS Romania 1st December 2015 http://www.cnlas.ro/images/doc/01122015_rom.pdf

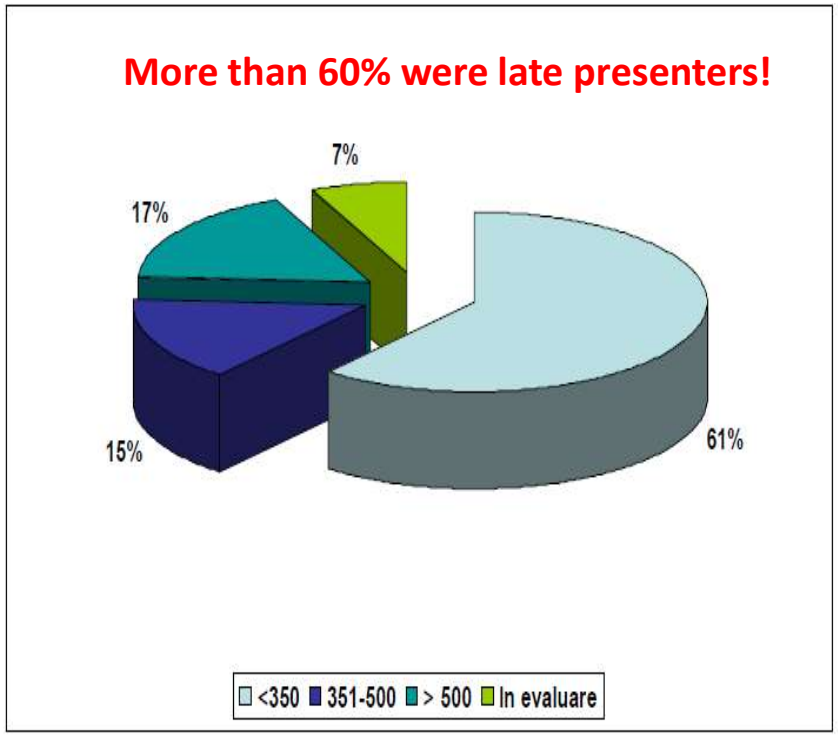
Trends of HIV transmission in Romania (2007 - 2016)



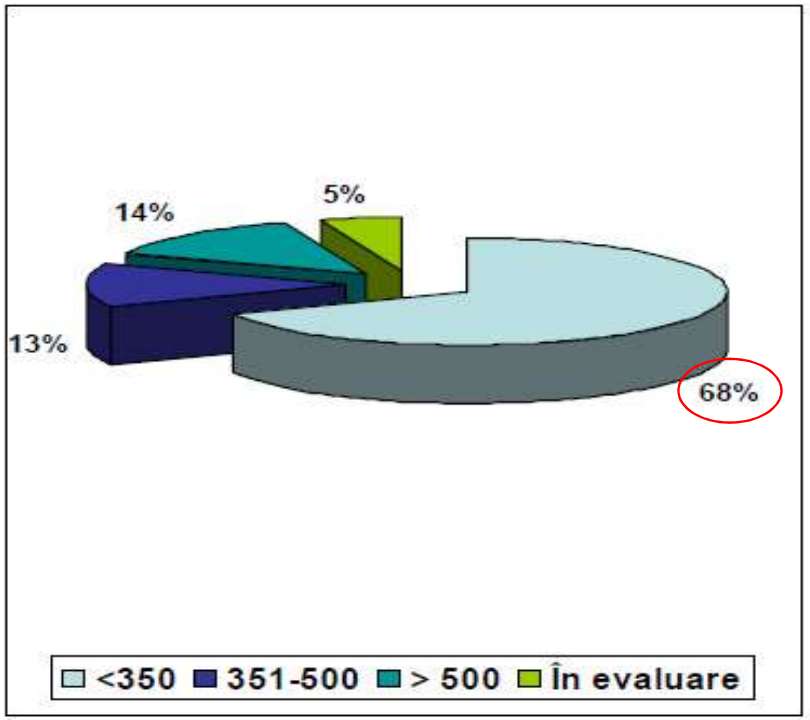
Source: Compartment for Monitoring and Evaluation of HIV/AIDS data in Romania, in National Institute for Infectious Diseases “Prof. Dr. Matei Bals”2016

Immunologic status in newly HIV diagnosed patients in 2016

More than 60% were late presenters!

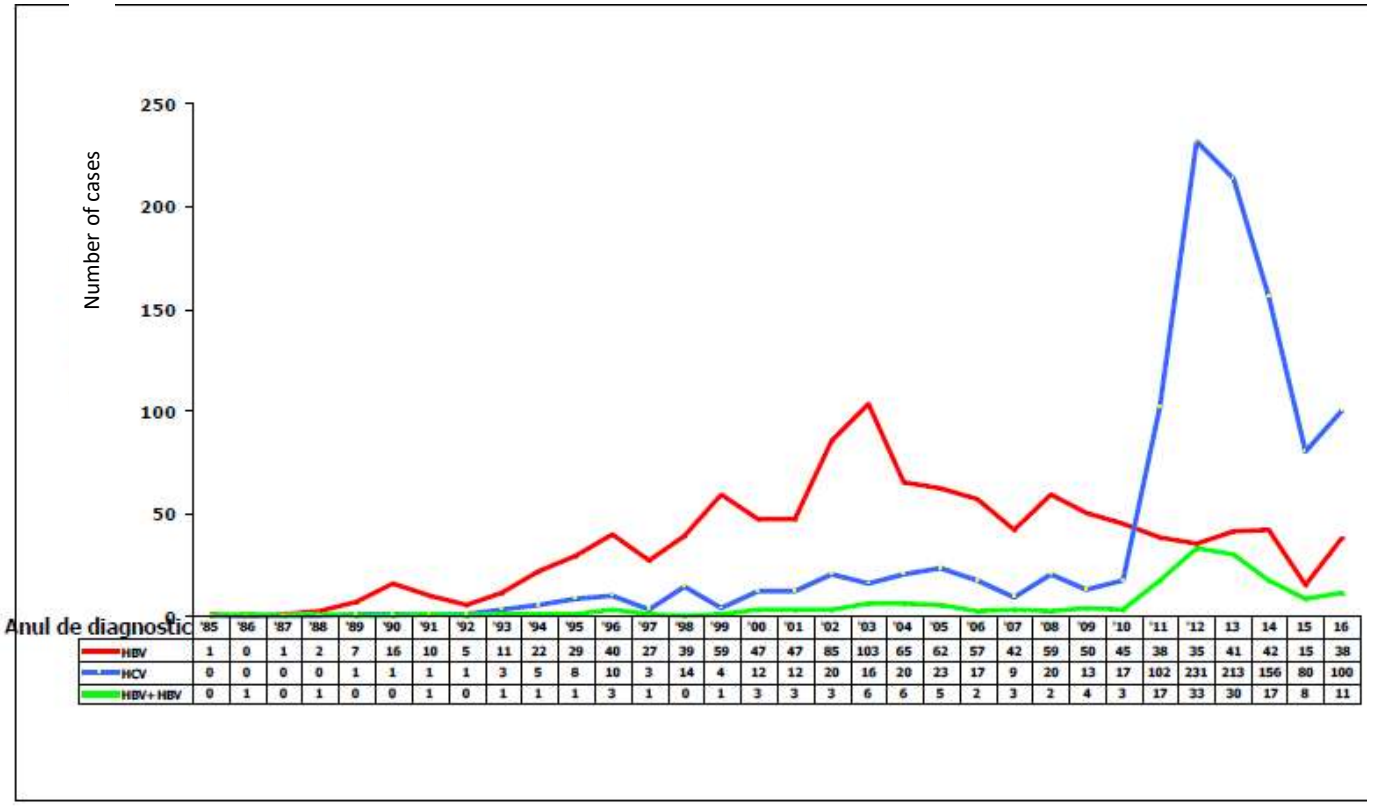


Immunologic status for intravenous drug users



Source: Compartment for Monitoring and Evaluation of HIV/AIDS data in Romania,
in National Institute for Infectious Diseases "Prof. Dr. Matei Bals"2016

HCV, HCV and HBV/HCV co-infection in HIV-positive patients in Romania (1985-2016)



Anul de diagnostic	'85	'86	'87	'88	'89	'90	'91	'92	'93	'94	'95	'96	'97	'98	'99	'00	'01	'02	'03	'04	'05	'06	'07	'08	'09	'10	'11	'12	13	14	15	16
HBV	1	0	1	2	7	16	10	5	11	22	29	40	27	39	59	47	47	85	103	65	62	57	42	59	50	45	38	35	41	42	15	38
HCV	0	0	0	0	1	1	1	1	3	5	8	10	3	14	4	12	12	20	16	20	23	17	9	20	13	17	102	231	213	156	80	100
HBV+HBV	0	1	0	1	0	0	1	0	1	1	1	3	1	0	1	3	3	3	6	6	5	2	3	2	4	3	17	33	30	17	8	11

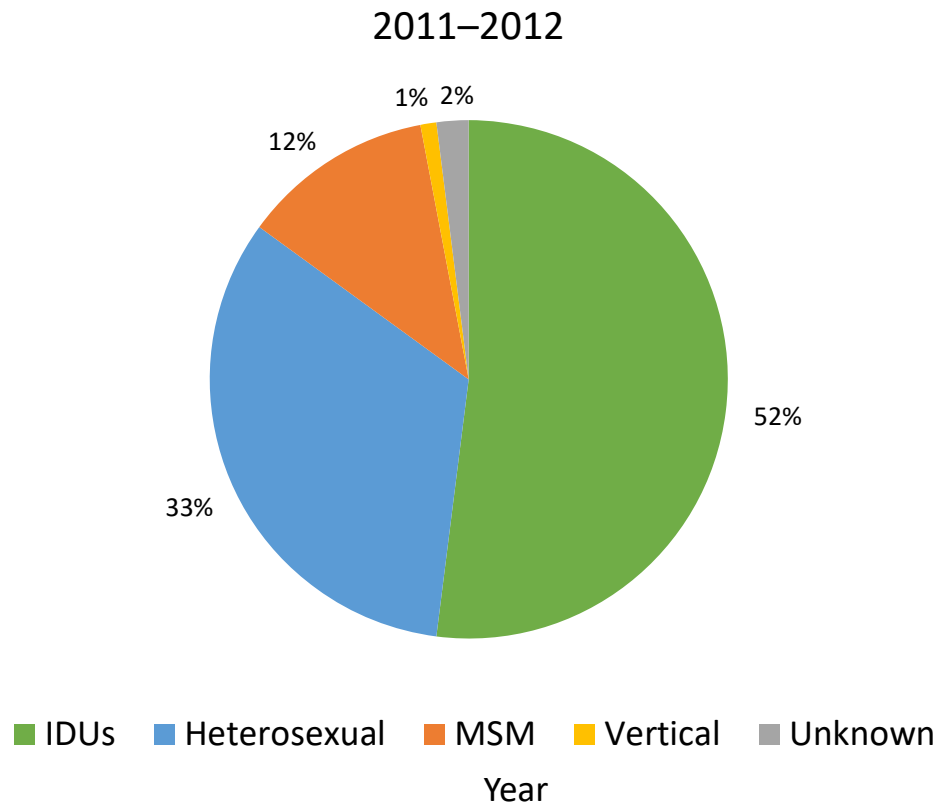
Source: Compartment for Monitoring and Evaluation of HIV/AIDS data in Romania, in National Institute for Infectious Diseases “Prof. Dr. Matei Bals”2016

Prevalence of HCV, HBV, TB and STIs in HIV-infected IDUs

Screened for	Number of patients with a positive test	%
HBs Ag	1/100	1.00%
HCV	82/100	82.00%
HBs Ag + HCV	9/100	9.00%
Syphilis	10/100	10.00%
TBC	37/100	37.00%

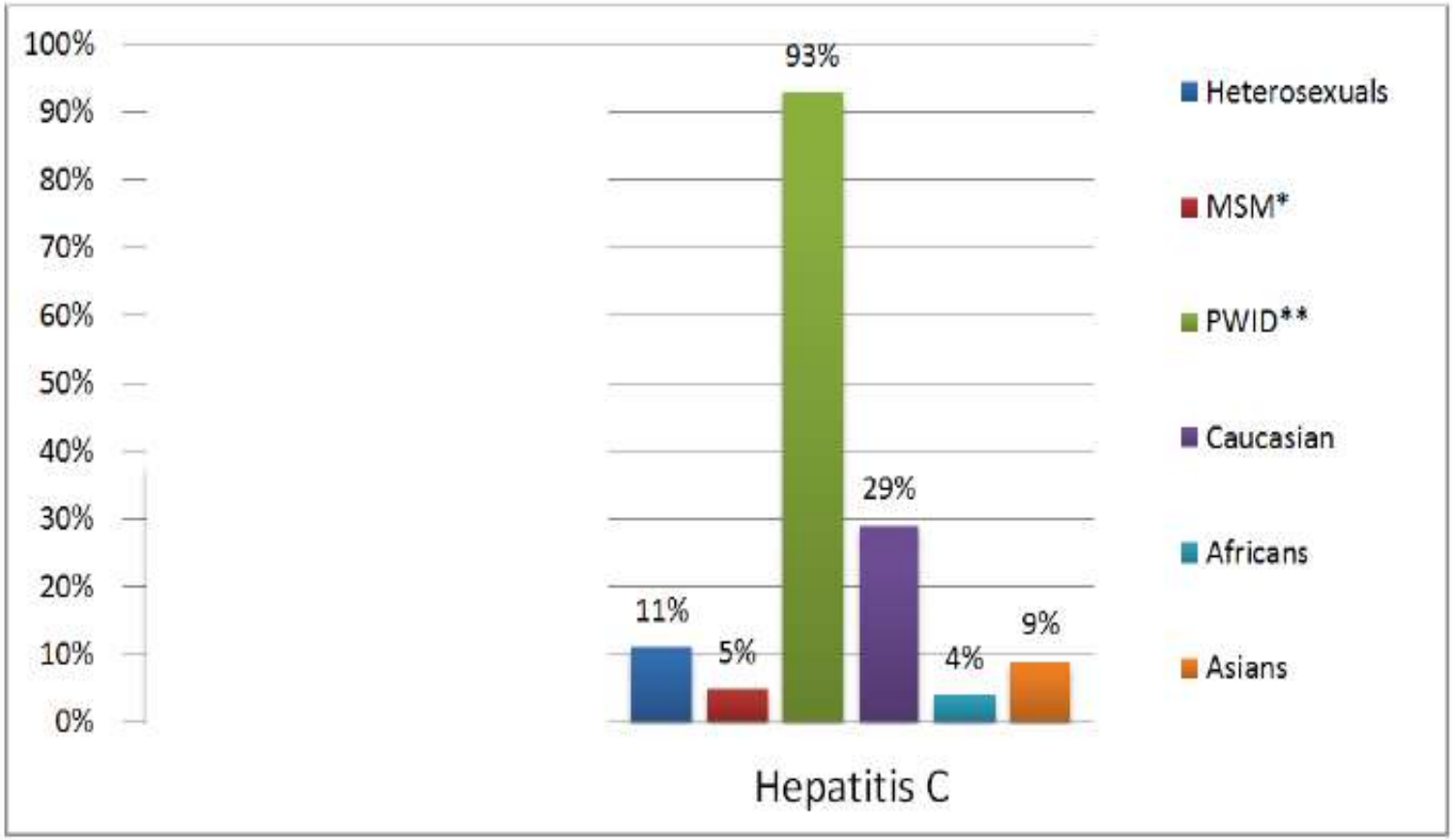
Source: Compartment for Monitoring and Evaluation of HIV/AIDS data in Romania, in National Institute for Infectious Diseases "Prof. Dr. Matei Bals"2016

Number of IDUs among newly HIV diagnosed cases in “Victor Babes” Clinical Hospital between 2007- 2015



Source: Statistics Department from “Victor Babes” Hospital Bucharest
*Oprea C et al. EACS 2013, 16–19 October, Brussels

Prevalence of HCV infection in patients from Swiss cohort (SHCS)



- Hahne et al BMC Inf Dis 2013

Diagnostic methods in HIV/HCV infected patients (1)

Chronic hepatitis C and screening for other types of hepatitis

- Anti HCV antibodies – may be detected between 1 and 6 months after infection and may be absent in severe immunosuppressed patients (rarely)
- HCV - RNA
- Test for HBsAg, Anti HBs antibodies and Anti HBc
- Test for IgG anti HAV antibodies

Diagnostic methods in HIV/HCV infected patients (2)

Evaluation of liver disease:

- Complete blood count, liver enzymes
- Staging of liver fibrosis using: liver biopsy, FibroScan, serological markers for fibrosis: (APRI, FIB4)
- Function of the liver (blood coagulation, albumin)
- Hepatic ultrasound: every 6 months for patients with cirrhosis
- Digestive endoscopy: at diagnosis and each 2 – 3 years for patients without esophageal varices

A HIV-infected patient with positive serology for HCV:

- NEEDS COUNSELING BOTH BEFORE AND AFTER TESTING
- NEEDS EVALUATION OF HCV VIRAL LOAD AND LIVER FIBROSIS STAGE
- IN CASE OF ADVANCED FIBROSIS, HIGH LEVEL OF LIVER ENZYMES, HIGH HCV VIRAL LOAD OR EXTRAHEPATIC MANIFESTATIONS – ANTIVIRAL TREATMENT IS INITIATED
- IN CASE OF POSITIVE SEROLOGY BUT WITH NONE OF THE ABOVE SIGNS – ONLY COUNSLING

What do we need to know before DAA treatment initiation?

- HCV **genotype**
- HCV **viral load** (HCV RNA)
- Resistant mutations for HCV (excepting genotype 1b) – only in particular cases/special situations
- **Fibrosis** stage (Fibroscan, biochemical markers– Fibromax, liver biopsy (puncture)

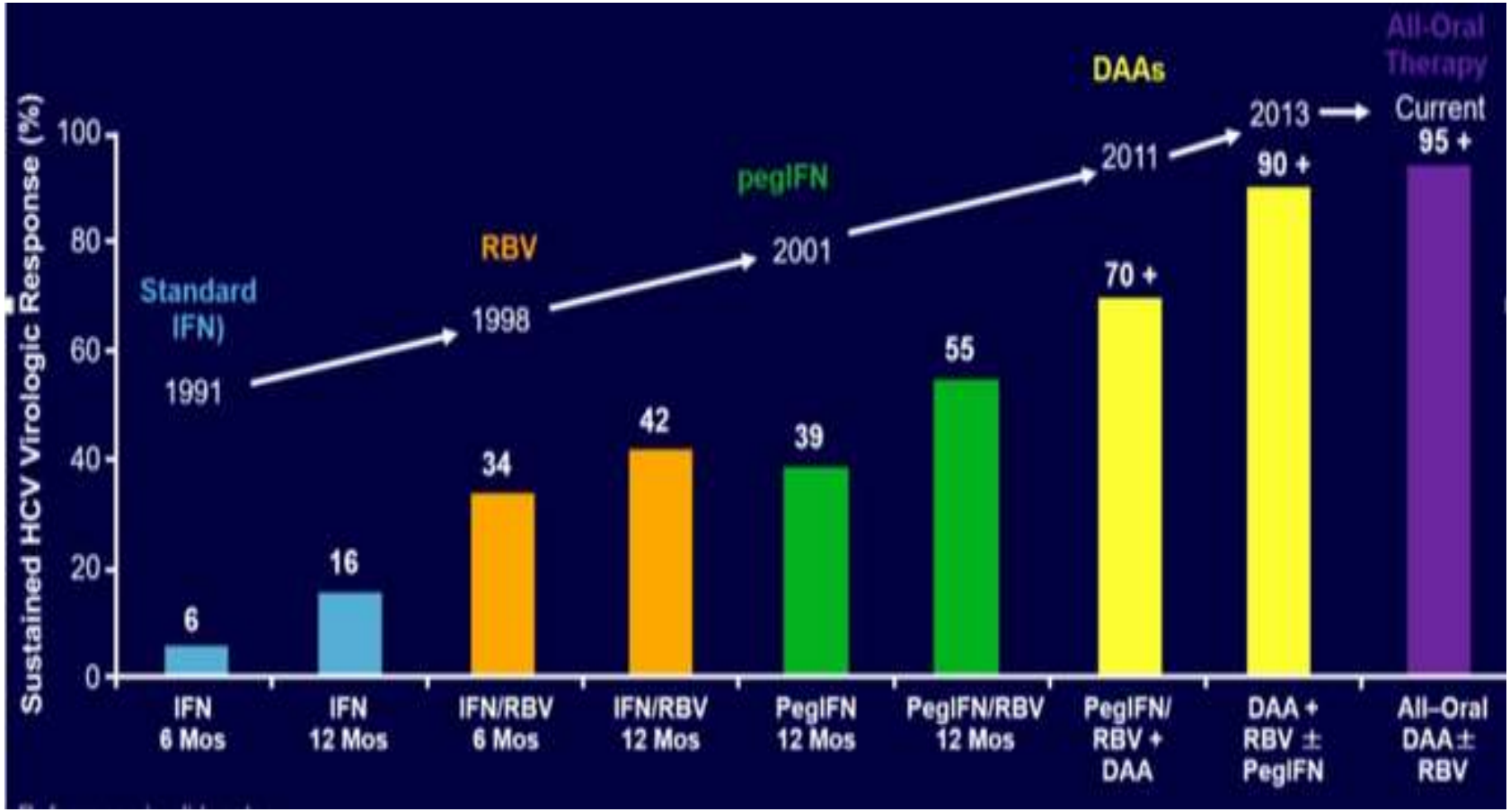
  - **cirrhosis** yes/no

    - **yes** – decompensation stage (Child- Pugh, ascites, encephalopathy)
    - decompensated cirrhosis – don't use protease inhibitors

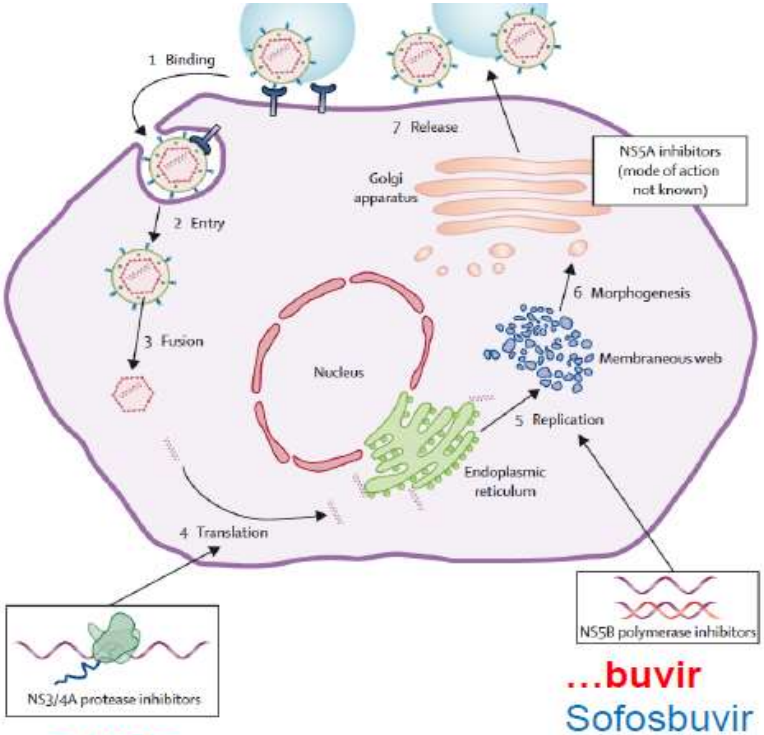
Previous treatment with IFN or DAA – virological response (yes/no)

- Anti HCV treatment – pay attention to drug - drug interaction with ART!
- Renal function evaluation: Creatinine clearance
- Immunologic and virological status in HIV-infected persons (CD4+, HIV-RNA)
- Fertile women (RBV has teratogenic effects!)

All anti HCV treatments are now efficient and well tolerated



Anti HCV medication: Mechanisms of action



…previr
Paritaprevir
Grazoprevir

…buvir
Sofosbuvir
Dasabuvir

…asvir
Daclatasvir
Ledipasvir
Ombitasvir
Elbasvir

Inhibitor Class	Reminder	Examples
Targeting HCV Protein Processing		
NS3/4A protease	PREVIR	▪ Grazoprevir, paritaprevir, simeprevir
Targeting HCV Replication		
NS5B polymerase	BUVIR	▪ Nucleos(t)ide: sofosbuvir ▪ Non-nucleos(t)ide: dasabuvir
NS5A	ASVIR	▪ Daclatasvir, elbasvir, ledipasvir, ombitasvir, velpatasvir

modif. after Manns, Cornberg, Lancet Inf Dis, 2013

Regimens approved by FDA for HCV treatment

	SMV ± SOF[2]	LDV/SOF[3]	DCV + SOF[4]	OBV/PTV/ RTV ± DSV[5,6]	EBR/GZR[7]	SOF/VEL[8]
Regimen Components						
• PegIFN	±					
• RBV	±	±	±	±	±	±
• NS5B nuc	± SOF	SOF	SOF			SOF
• NS5B non-nuc				± DSV		
• NS3/4 PI	SMV			PTV	GZR	
• NS5A		LDV	DCV	OBV	EBR	VEL
FDA Approval by HCV Genotype						
• GT1	✓	✓	✓	✓	✓	✓
• GT2						✓
• GT3			✓			✓
• GT4	✓	✓		✓	✓	✓

Therapeutic regimens for HIV/HCV co-infected patients

Genotip VHC	Regim terapeutic	Durata tratament la non-cirotici (sapt)	Durata tratament in CH compensata	Durata tratament in CH decompensata
1 si 4	SOF+ SMP± RBV	12 s fara RBV	12 s + RBV 24 s fara RBV	Nu se recomanda
	SOF/LDP ± RBV	12 s fara RBV	12 s + RBV sau 24 s fara RBV la cirotici sau pre/post-transplant 12 s + RBV sau 24 s fara RBV la cirotici sau pre/post-transplant	
	SOF+ DCV ± RBV	12 s fara RBV		
	OBV/PTV/r + DSV	12 s in GT1b	Nu se recomanda	
	OBV/PTV/r + DSV + RBV	12 s in GT1a	12 s in GT1b 24 s in GT 1a	Nu se recomanda
	OBV/PTV/r + RBV	12 s in GT4	24 s in GT4	Nu se recomanda
	EBR + GZP*	12 s		
	SOF/VEL*	12 s		
2	SOF + DCV± RBV	12 s fara RBV	16-24 s fara RBV	12 s + RBV
	SOF + RBV	12 s	16- 20 s	
	SOF/VEL*	12s		
3	SOF + PEG-IFN/RBV	Nu se recomanda	12 s la cei eligibili pt IFN	Nu se recomanda
	SOF + RBV	24 s	Nu se recomanda	
	SOF + DCV± RBV	12 s fara RBV	24 s + RBV	
	SOF/ VEL*	12 s	12 s	
5	SOF/LDP	12 s	12 s	
	SOF/VEL*	12 s		

EASL/ AASLD guidelines 2016

HCV genotype 1b: treatment recommendations for naïve patients

Without cirrhosis – treatment duration: 12 weeks

- **Sofosbuvir/Ledipasvir**
- **Elbasvir/Grazoprevir**
- Sofosbuvir/Velpatasvir
- **Ombitasvir/Paritaprevir/ritonavir/ Dasabuvir**
- Sofosbuvir/Daclatasvir
- Simeprevir/ Sofosbuvir

Compensated cirrhosis – treatment duration: 12 weeks

- **Sofosbuvir/Ledipasvir**
- **Elbasvir/Grazoprevir**
- Sofosbuvir/Velpatasvir
- **Ombitasvir/ Paritaprevir/ritonavir/ Dasabuvir**

AADLD/ IDSA guidelines 2016

HCV genotype 3: treatment recommendations for naïve patients

Without cirrhosis – treatment duration: 12 weeks

- Sofosbuvir/Velpatasvir
- Sofosbuvir/Daclatasvir

Compensated cirrhosis – treatment duration: 12 weeks

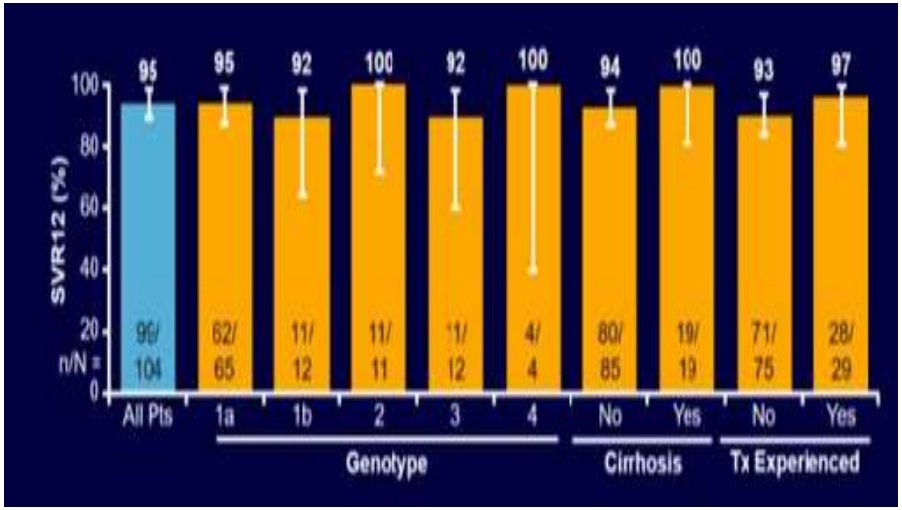
- Sofosbuvir/Velpatasvir - 12 sapt
- Sofosbuvir/Daclatasvir +/- RBV - 24 sapt daca exista mutatii de rezistenta (Y 93H)

AADLD/ IDSA guidelines 2016

Studies regarding new therapeutic regimens in HIV/HCV co-infected patients

ASTRAL 5 – Sofosbuvir/Velpatasvir 12 s

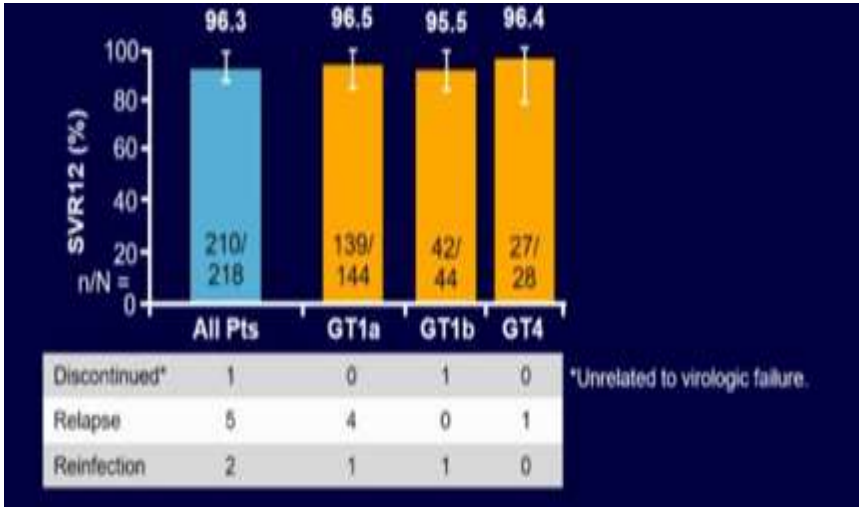
N = 106



Wyles D, EASL 2016

C- EDGE (GRAZOPREVIR/ ELBASVIR)

N = 218



Rockstroh JK et al, Lancet HIV 2015

Treatment duration and monitoring in HIV/HCV co-infected patients

- Treatment duration: is similar to mono- infected patients - 12 weeks

Treatment duration **shorter than 12 weeks is NOT recommended** in **HIV/HCV co-infected patients, black individuals and in those with IL28b CT/TT polymorphism**

(AASLD/ IDSA guidelines 2016)

- Treatment monitoring:

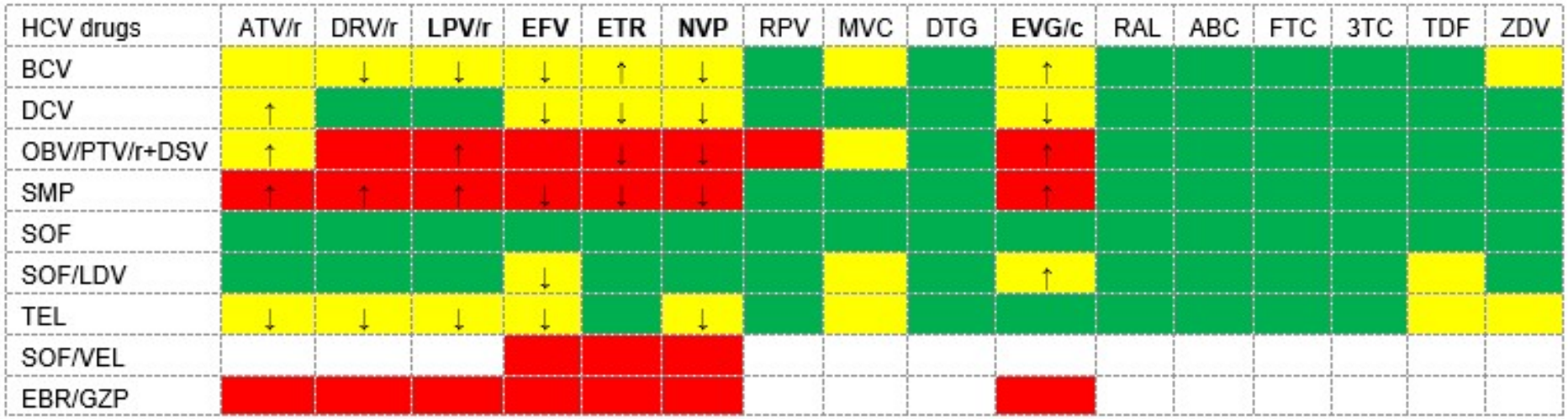
Complete blood count, liver enzymes

Renal function

HCV-RNA evaluation after 4 weeks (!) and after **12** (+/- 24) **weeks** after DAA treatment is completed

CD4 cell count and HIV – RNA evaluation (each 3 months)

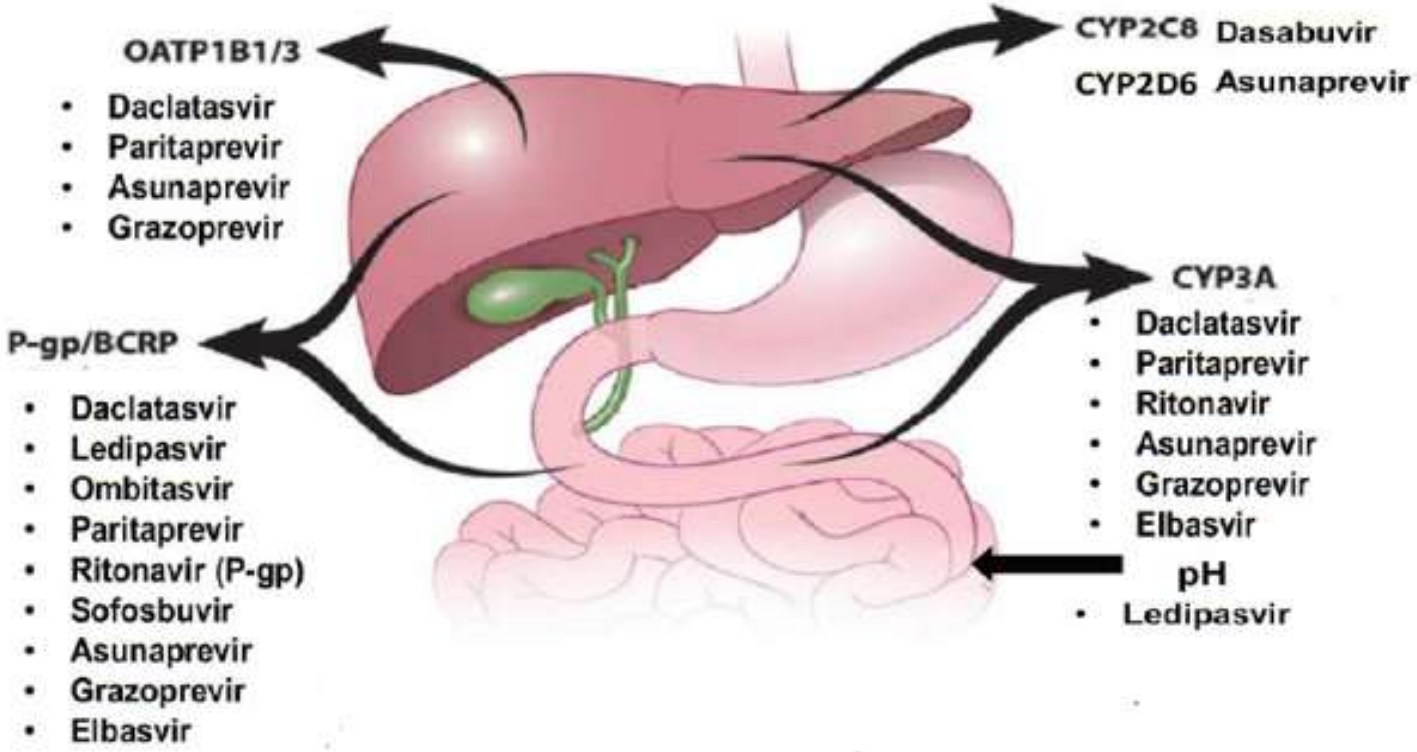
Drug – drug interactions between antiretroviral treatment and Direct-Acting Antiviral drugs (DAA)



ATV/r = atazanavir/ritonavir
DRV/r = darunavir/ritonavir
LPV/r = lopinavir/ritonavir
RTV= ritonavir
EFV= efavirenz
ETR= etravirina
NVP = nevirapina
RPV = rilpivirina
MVC= maraviroc

DTG= dolutegravir
EVG/c = elvitegravir/ cobicistat
RAL = raltegravir
ABC = abacavir
FTC= emtricitabina
3TC = lamivudine
TDF = tenofovir
ZDV = zidovudine

Liver metabolism of antiviral drugs



Dick T et al, Hepatology 2015

Drug – drug interactions HIV/HCV

	SMV + SOF	SOF	LDV/SOF	DCV + SOF	OMV/PTV/RTV + DSV
Atazanavir + RTV	X	√	≈	≈	√
Darunavir + RTV	X	√	≈	√	X
Lopinavir/RTV	X	√	≈	√	X
Tipranavir + RTV					
Efavirenz					
Rilpivirine					
Etravirine	≈	√	√	≈	≈
Raltegravir	√	√	√	√	√
Elvitegravir + COBI	X	≈	≈	≈	≈
Dolutegravir	√	√	√	√	√
Maraviroc	√	√	√	√	≈
Tenofovir DF	√	√	≈ nephrotoxicity	√	√

http://www.hiv-druginteractions.org

No clinically significant interaction expected

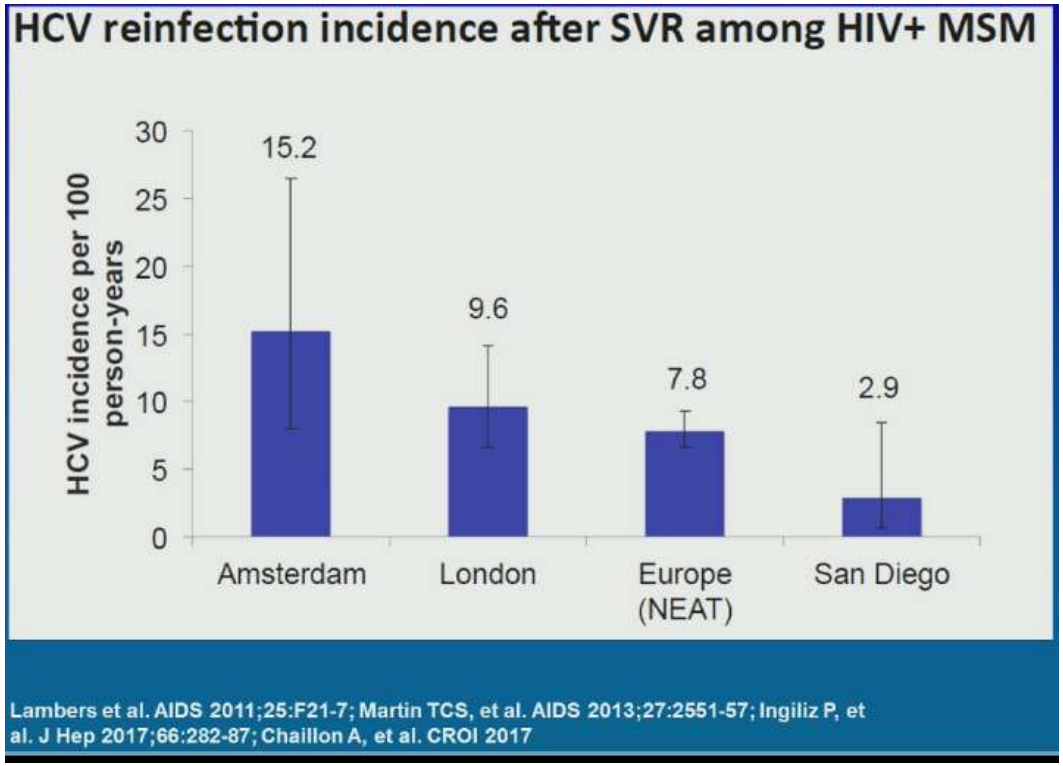
Potential interaction may require adjustment to dosage, timing of administration, or monitoring

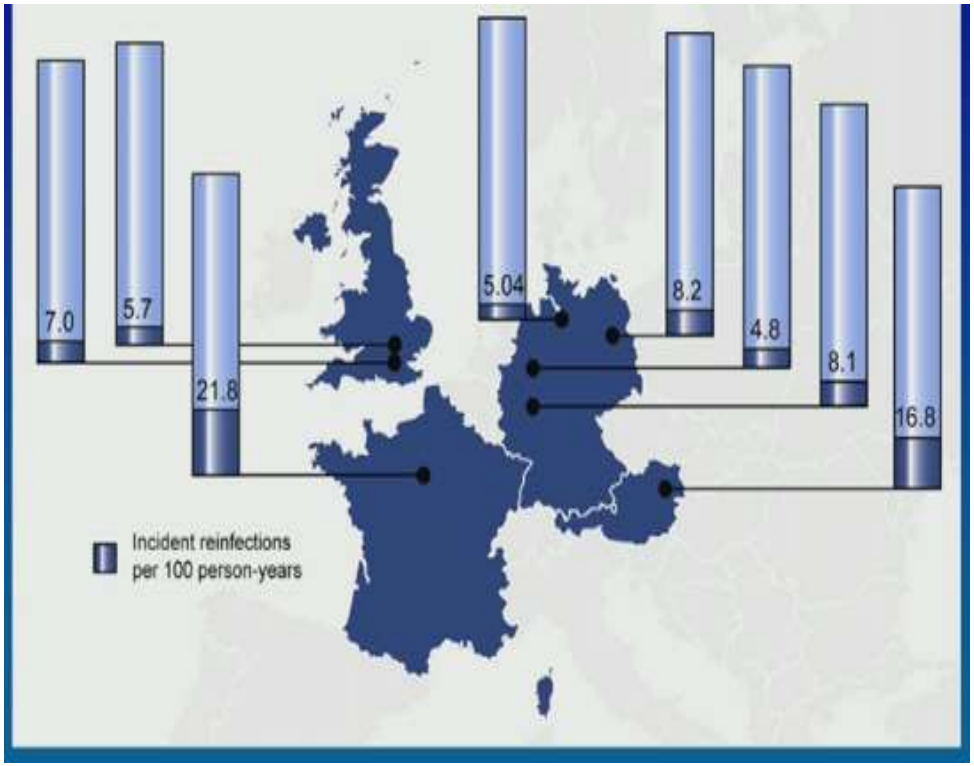
Do not coadminister

Pay attention to special situations!!

- Risk of HBV reactivation at 4 – 8 weeks after DAA treatment initiation *(29 de cases of reactivation - Bersoff- Matcha SJ AASLD 2016- LB 17)*
- Patients treated with regimens containing VEL or LDV and concomitant cART (based on TDF) need periodical monitoring of the renal function; this combination has to be avoided in case of creatinine clearance **< 60 ml/min**
- Recommendations for patients with impaired renal function (Creatinine clearance< 30 ml/min) and genotype 1b: Ombitasvir/Paritaprevir/ritonavir/Dasabuvir, for genotype 1a, 1b or 4: Elbasvir/Grazoprevir
- The risk of HCC may persist after DAA treatment *(Romano A AASLD 2016)* - screening for hepatic carcinoma is still recommended after DAA treatment (hepatic ultrasound twice/year)
- Risk of re-infection in intravenous drug users or MSM patients *(Lambers FA – AIDS 2011, Ingiliz et al Journal of Hepatology 2017)*

Risk of re-infection in MSM patients





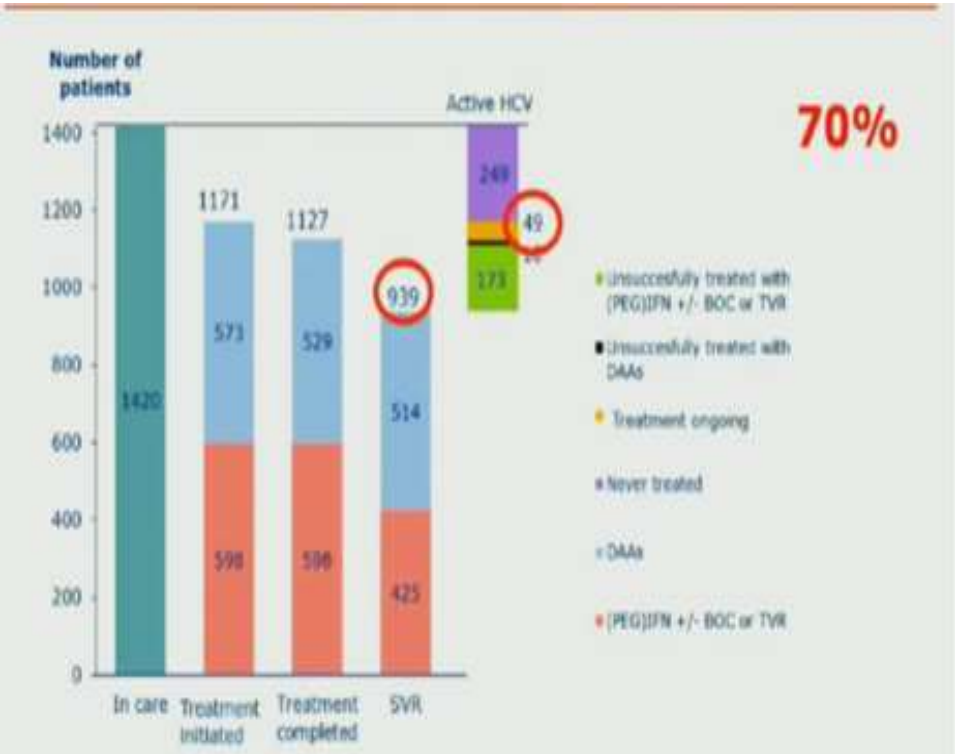
Ingiliz et al Journal of Hepatology 2017)

“Treatment as prevention” in HCV

study from Netherlands

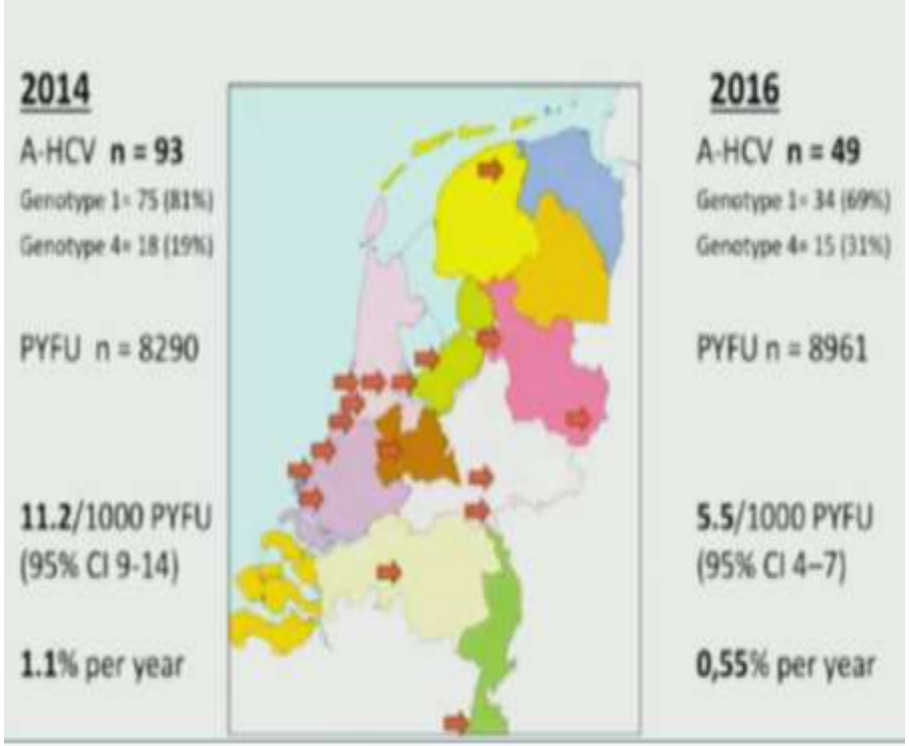
Athena Cohort –DAA treatment with no restrictions

HCV cascade of care



Reduced risk of HCV transmission

Results

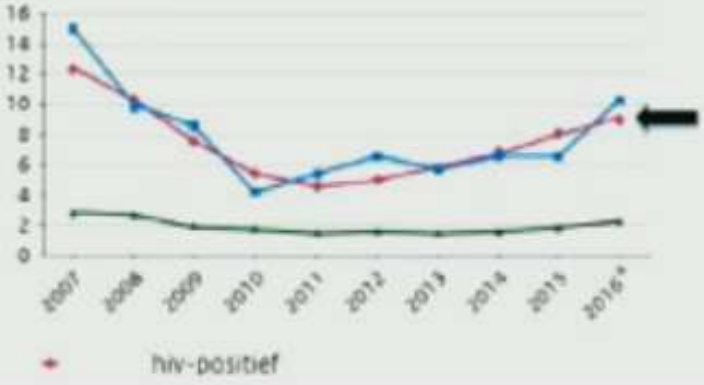


Syphilis and STD evolution

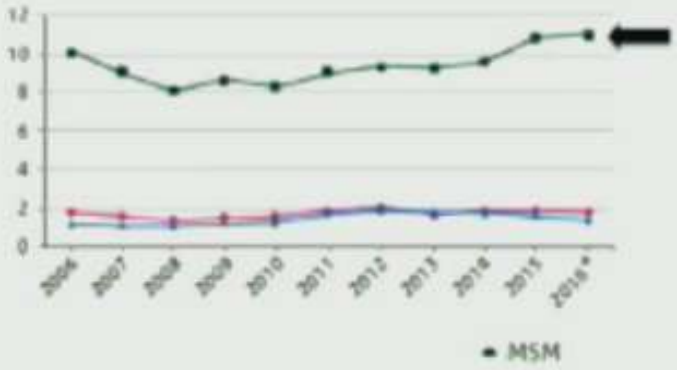
First six months of 2015:
N=446 syphilis infections diagnosed

First 6 months of 2016:
N=629 syphilis infections diagnosed (=41% increase ! 95% in MSM)

Syphilis in HIV+MSM

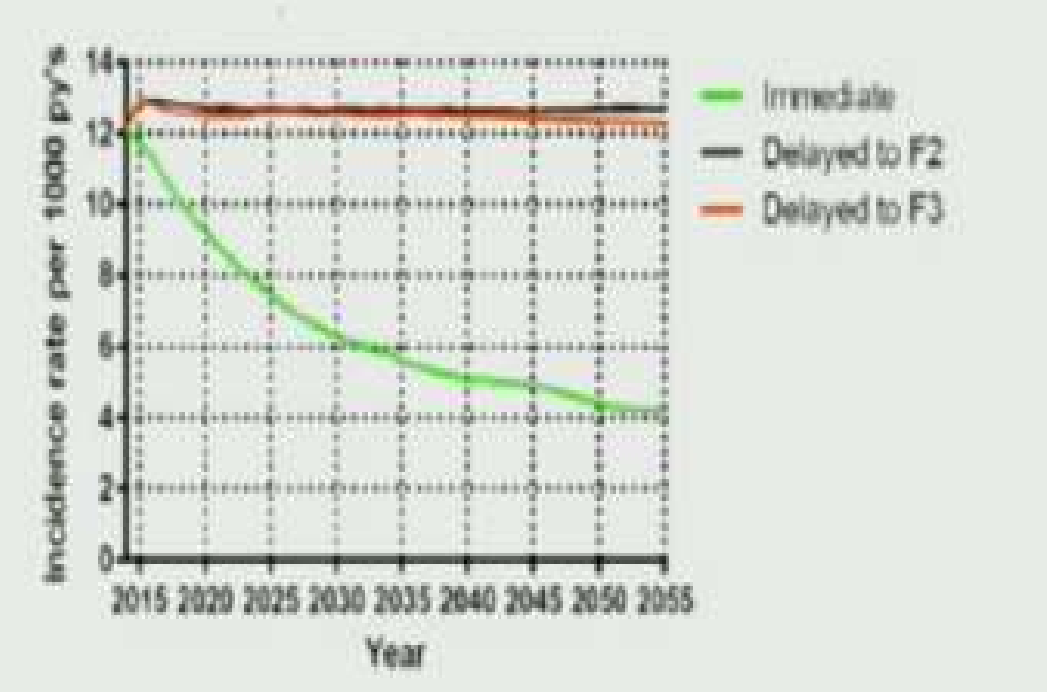


LGV in MSM



“Treatment as prevention”- Will it also work for HCV?

Dutch modelling study
Immediate initiation of DAA treatment is cost –efficient and may reduce (but not eliminate) the risk of HCV transmission among MSM



Hullegie SJ et al P 526 - CROI 2016

The role of GPs in the management of HCV-infected patient

Primary prevention methods

Counseling regarding the risk of transmission of viral hepatitis viruses (B, C, D) by iv drugs and sexual contacts

Secondary prevention methods

Links patients to centers where HCV test, disgnosis and treatment is available

Gives indications about how to change the life style, diet, alcohol

Immunizations

Evaluation of psycho-social problems

Tertiary prevention methods

Psycho-social support

Education

DAA treatment monitoring

Barry et al. Ir J Med Sci, 2004.

Take home messages

- In the last years a remarkable progress in diagnosis and treatment of chronic HCV was achieved.

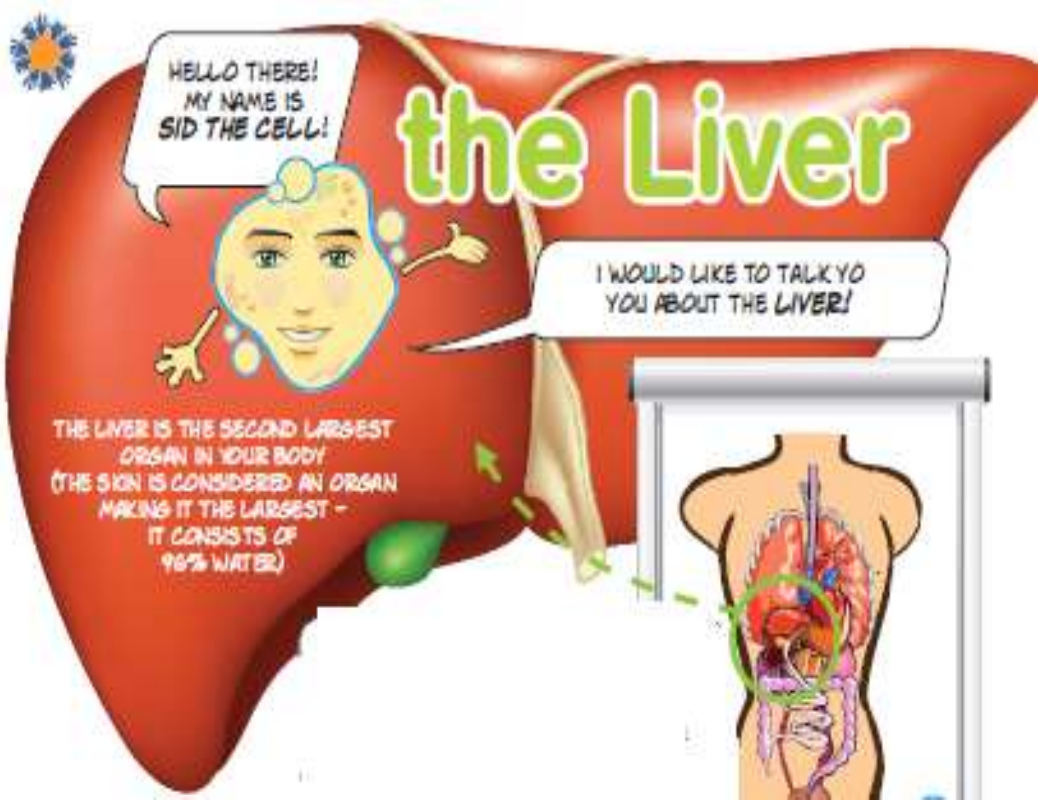
  SVR with the new antiviral regimens (DAAs) – 95%
- The response to DAAs is **similar** for HCV mono-infected and HIV/HCV **co-infected** patients
- HIV/HCV co-infected patients need drug-drug interaction evaluation
- Treatment duration shorter than 12 weeks is not recommended in HIV/HCV co-infected patients.

Take home message

- **IDUs** and **MSM** patients have a higher risk of HCV re-infection
- Even if the risk of liver disease progression is lower in patients with sustained virologic response and they have a higher quality of life, these patients still need to be monitored for hepatic carcinoma
- The rate of HCV transmission may be reduced if universal treatment will be available ("**treatment as prevention" for HCV**)
- The magnitude of HCV infection may be reduced by :

- **Intensifying screening programmes for HCV detection** (HEPCARE EUROPE)
- **Active management for HCV-infected patients** (including those from vulnerable groups)

Thank you!


HELLO THERE!
MY NAME IS
SID THE CELL!
the Liver
I WOULD LIKE TO TALK YO
YOU ABOUT THE LIVER!
THE LIVER IS THE SECOND LARGEST
ORGAN IN YOUR BODY
(THE SKIN IS CONSIDERED AN ORGAN
MAKING IT THE LARGEST -
IT CONSISTS OF
98% WATER)