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BHIVA ‘Best of CROI’ Feedback Meetings

London | Edinburgh

Wakefield | Cardiff

Birmingham | Haydock

Newcastle

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HIV/hepatitis and comorbidities

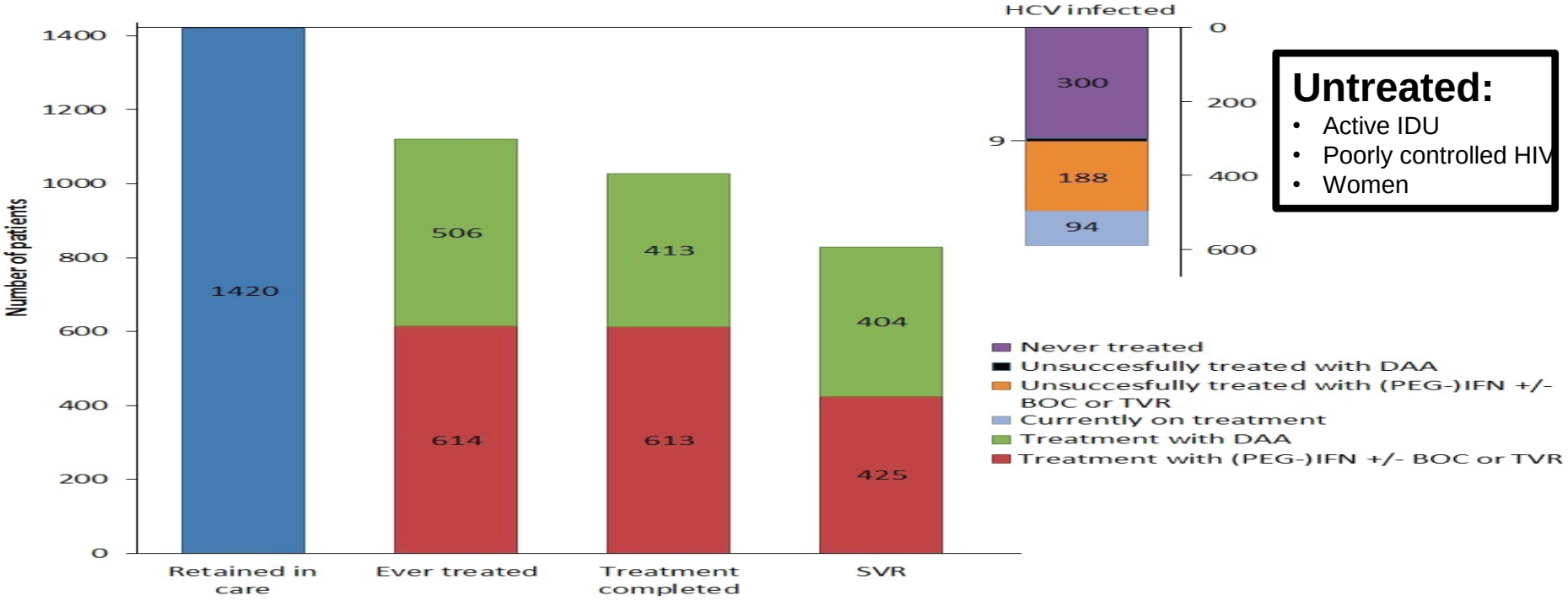
- Access to DAA-based treatment for HCV
- Responses in HIV/HCV co-infected patients from ‘Real World’ cohorts
- Does ‘Treatment as Prevention’ work for HCV?

- Fatty liver – the new frontier for liver disease?

- Comorbidities – Brain, thrombosis, kidneys and aging

Rapid uptake and success in the Netherlands (Boerekamps, O136)

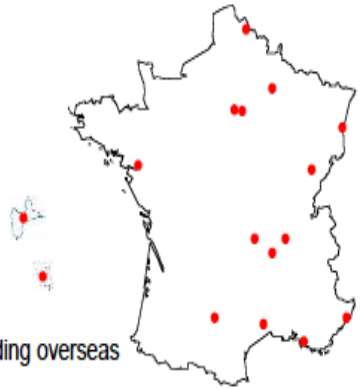
- >1400 co-infected patients in the Netherlands
- Access to DAA therapy 2014-2016 – restricted to F3/F4
- 2016 – access for all



High uptake in DatAIDS, France

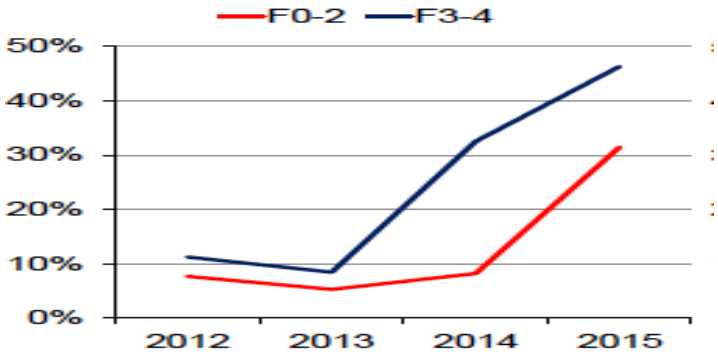
(Cotte et al, P550)

Dat'AIDS Cohort

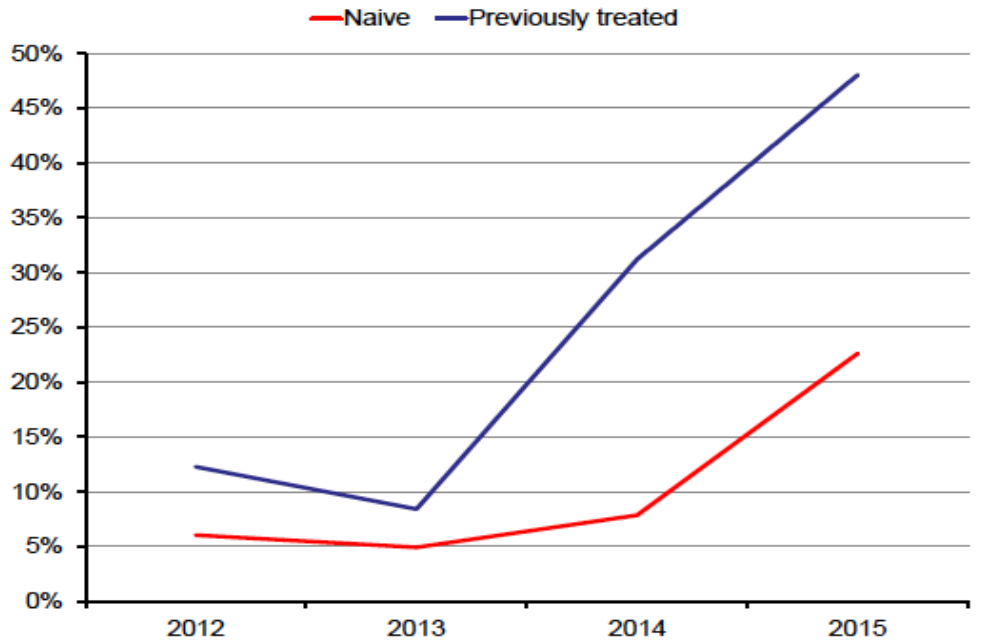


16 French HIV centers, including overseas

25% of HIV-infected patients under care in France



Treatment initiation rate



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High uptake in DatAIDS, France

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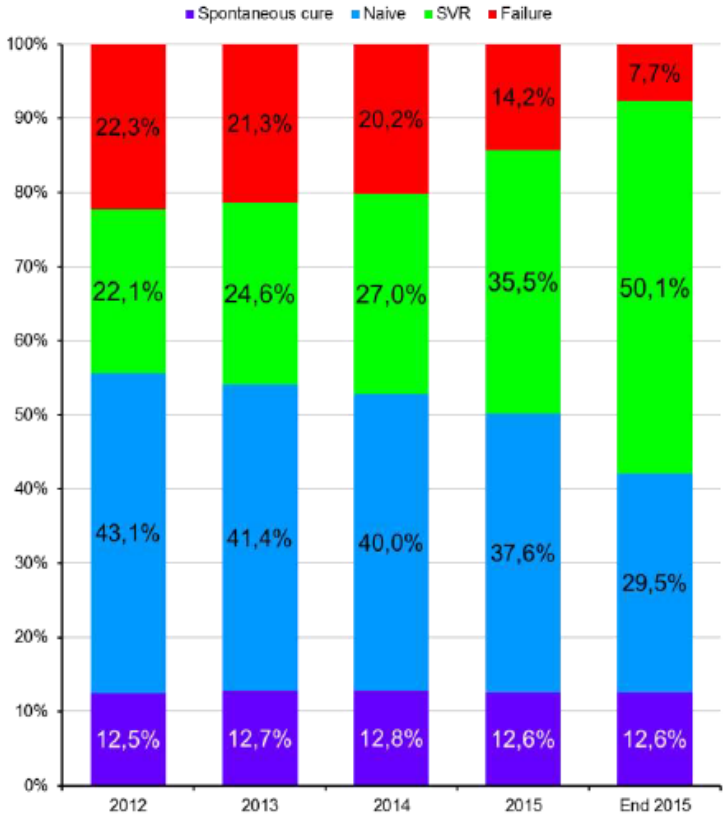

- >65% of HIV/HCV co-infected patients treated by 2015
- ~60% have achieved SVR12 or spontaneously cleared virus

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Generic DAAs via Buyers Clubs (A Hill, et al P569)

- 1150 patients with HCV from Australia, China, Russia, SE Asia accessed DAAs via Buyer's Clubs
- SOF/R/LDV/DCV and more recently VEL from suppliers in India, Egypt, Bangladesh and China

Figure 1: Patients by genotype

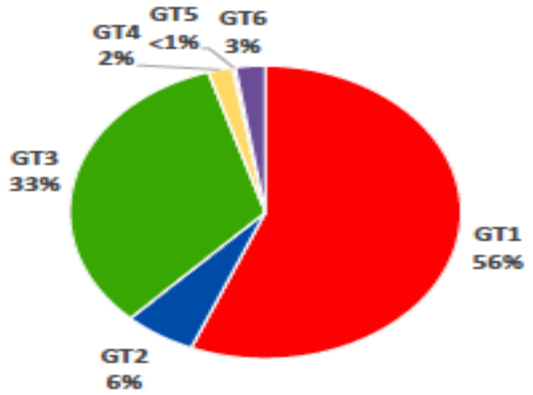
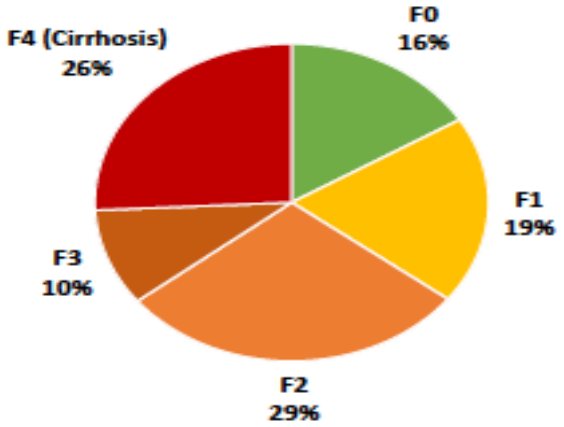


Figure 2: Fibrosis scores of patients



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Generic DAAs via Buyers Clubs (A Hill, et al P569)

Table 1: Baseline Characteristics

Patients	SOF & SOF/RBV N=100	SOF/DCV N=545	SOF/LDV N=502
% Male	79 % (79/100)	57 % (321/545)	57 % (288/502)
% Cirrhosis	16 % (16/100)	20 % (111/545)	16 % (78/502)
% GT 1	35 % (35/100)	31 % (168/545)	87 % (439/502)
% GT 3	46 % (46/100)	58 % (314/545)	4 % (19/502)
+ RBV	65 % (65/100)	7 % (81/545)	5 % (57/502)
12 weeks or less‡	41 % (41/100)	66 % (363/545)	79 % (398/502)
24 weeks or more*	38 % (38/100)	21 % (114/545)	11 % (55/502)

Figure 3: SVR4 responses by genotype

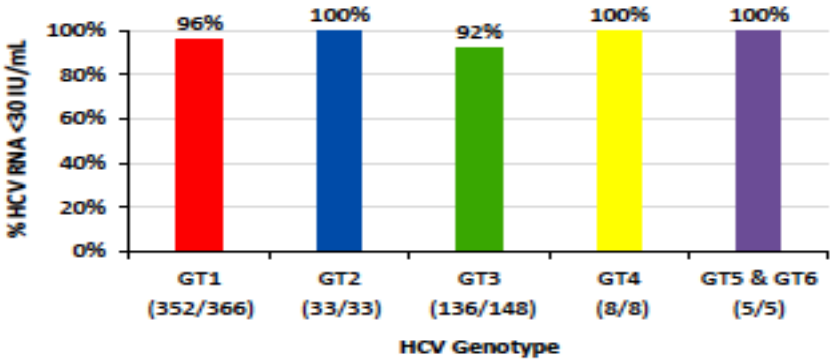
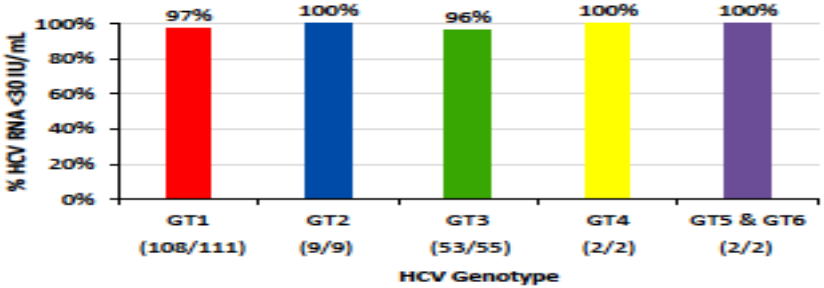


Figure 4: SVR12 responses by genotype*



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HCV DAA access – take home messages

- Access to DAAs increasing across Western Europe
- Buyer's clubs are a genuine option for many patients

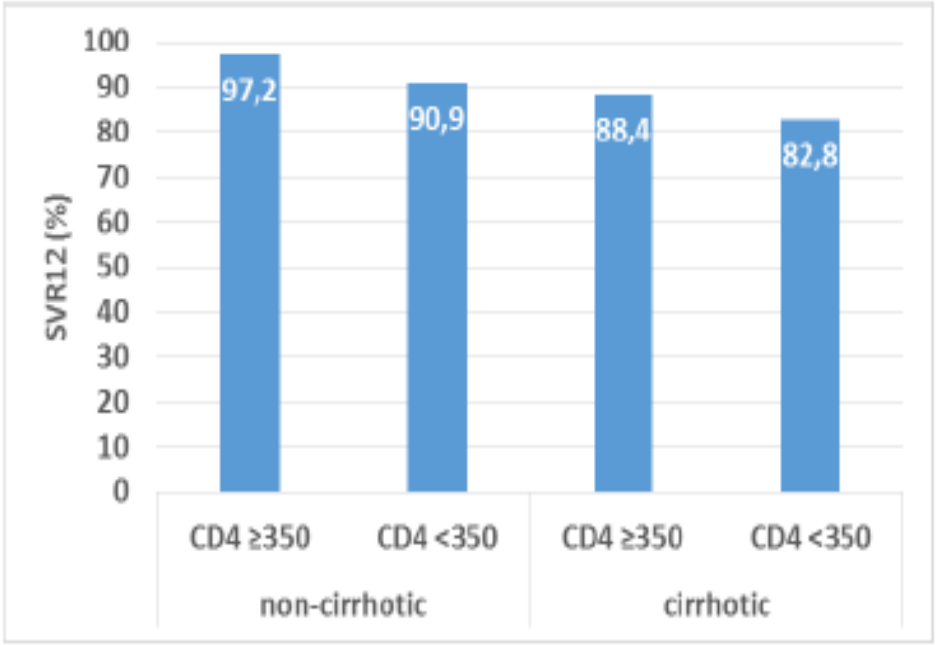
GECCO – high SVR12 rates for co-infected patients – effect of CD4 counts?

(Boesecke, et al P551)

Table 1. Baseline characteristics

	All n=1505	HCV mono n=1156	HCV/ HIV n=349	p-value
Male sex [%]	63	55	89	≤0.001
Median age [years] (IQR)	52 (45-59)	54 (46-61)	48 (42-53)	0.085
HCV GT 1/2/3/4 [%]	72/4/18/6	73/3/21/3	70/3/9/18	≤0.001
Baseline HCV-RNA >6 Mio. IU/ml [%]	20	17	27	≤0.001
Median baseline ALT [U/l] (IQR)	67 (43-111)	67 (42-111)	65 (43-109)	0.982
Treatment-experienced [%]	46	45	52	0.107
Liver cirrhosis [%]	29	31	22	0.003
OST [%]	19	18	21	0.309

Figure 1. SVR12 according to cirrhosis status and CD4 T cell count (/ul)



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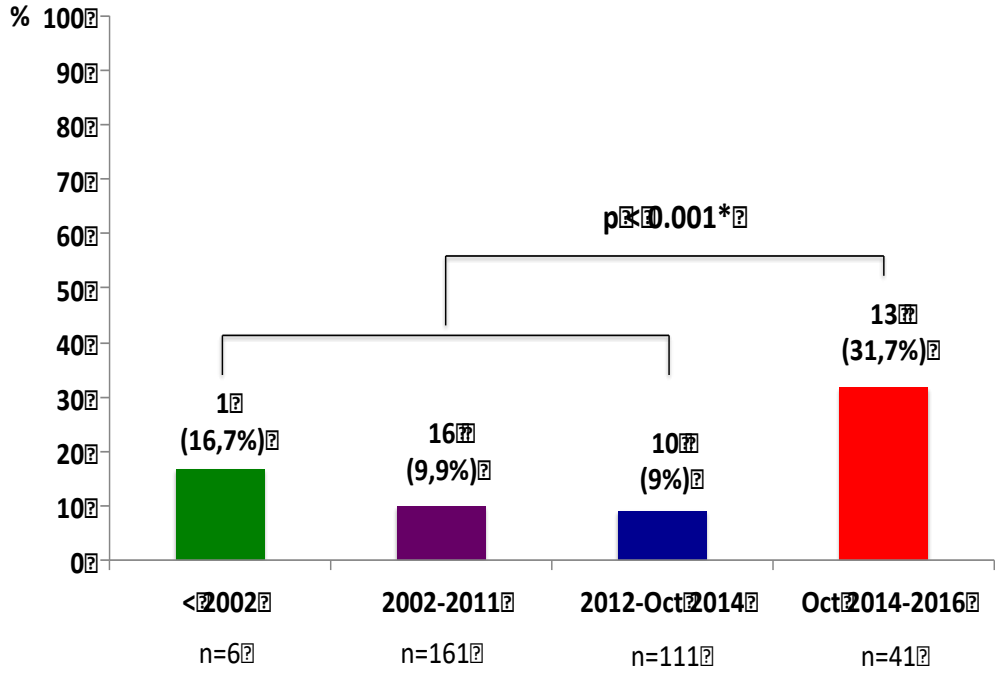
Hepatocellular carcinoma after SVR with IFN-free regimens in HIV/HCV-coinfection (N Merchante, et al, 0139)



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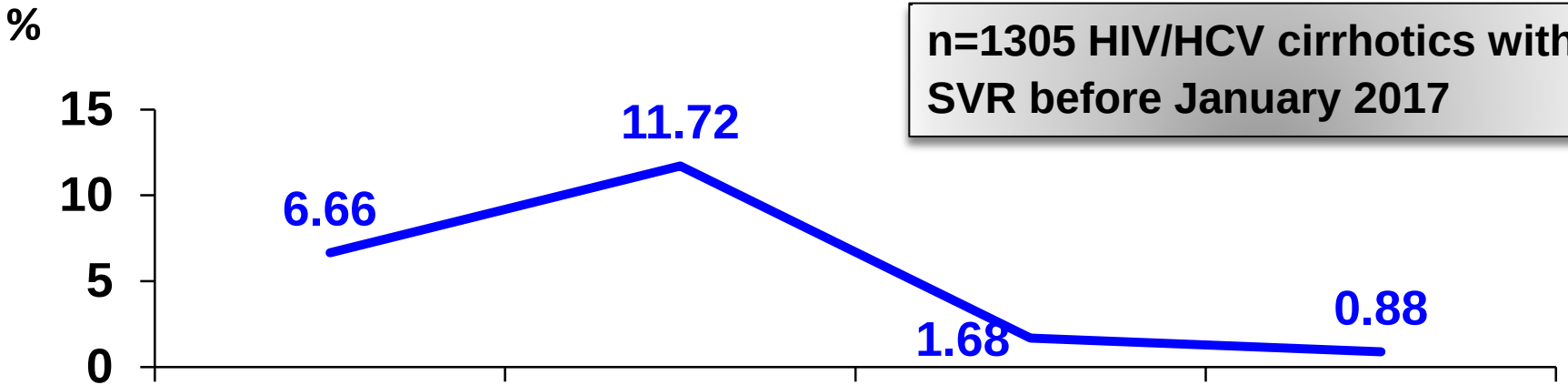
Results (IV): Analysis 2

Frequency of HCC diagnosis after SVR in HIV/HCV-coinfected patients with cirrhosis

GRUPO DE ESTUDIO DE HEPATITIS VÍRICAS - SEIMC

19 centers from the GEHEP-002 cohort reported data of the number of HIV/HCV-coinfected patients with cirrhosis who achieved SVR in each period.

n=1305 HIV/HCV cirrhotics with SVR before January 2017



	IFN	PEG-IFN + RBV	DAA + PR	DAA IFN free
HCC after SVR	1	17	4	8
No. with SVR	15	145	238	907

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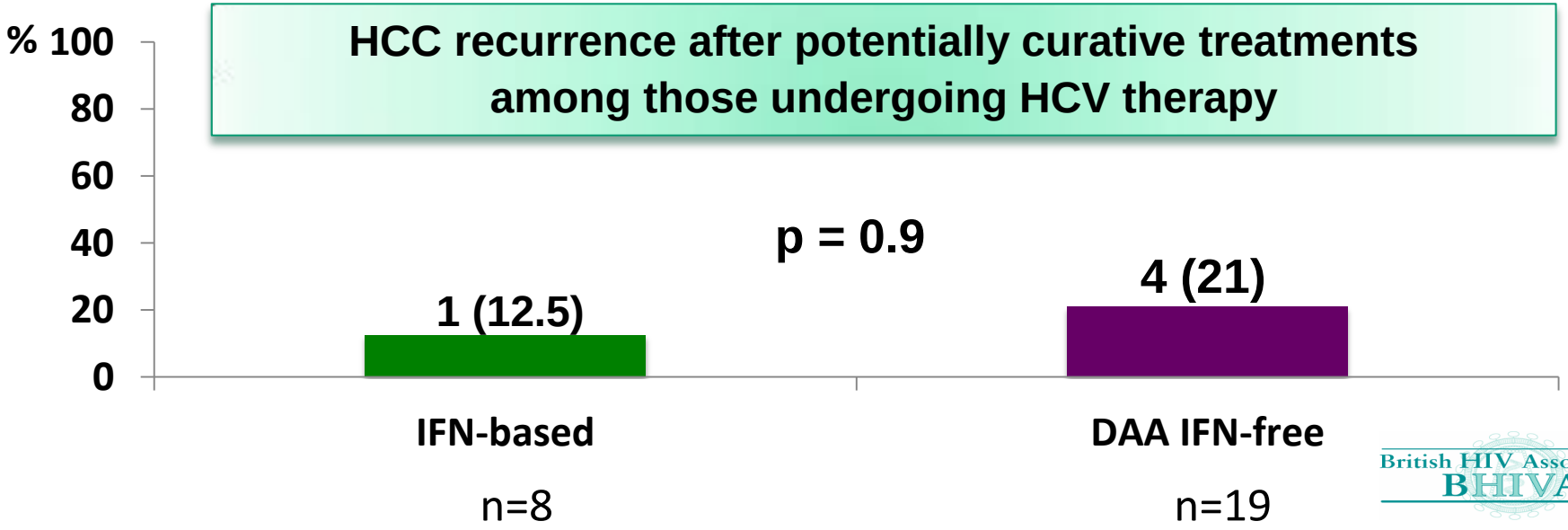
Results (V): Analysis 3

HCC recurrence after therapy against HCV

GRUPO DE ESTUDIO DE HEPATITIS VÍRICAS - SEIMC

39 patients with HCC received therapy against HCV after HCC diagnosis

- n=8 IFN-based. All of them after HCC curative therapies.
- n=31 DAA IFN-free.
  - n=19 with previous curative therapies against HCC and ultrasound evidence of lack of nodules prior to HCV therapy.



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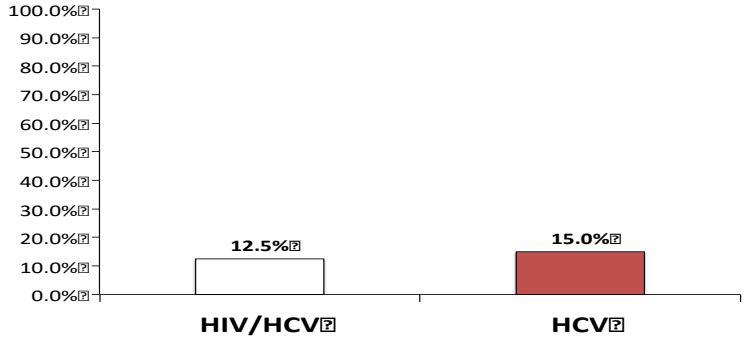
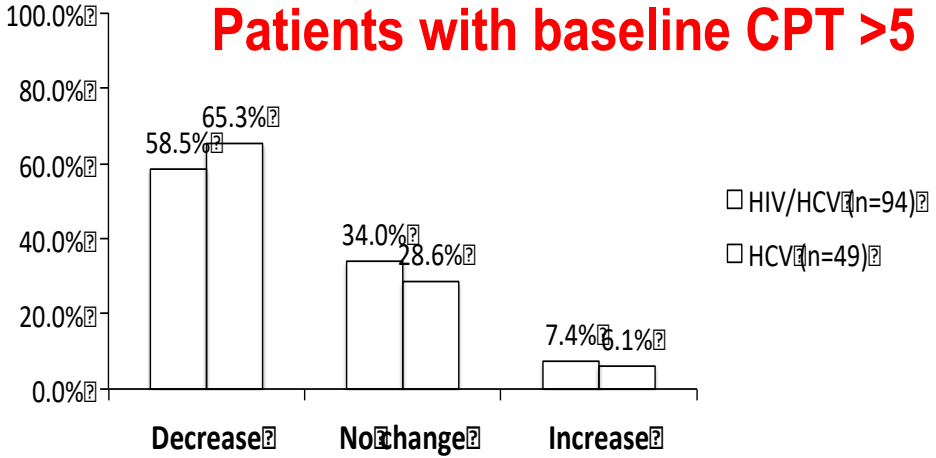
Influence of HIV on cirrhosis changes after successful Rx of HCV in co-infected patients (Macias, et al P536)

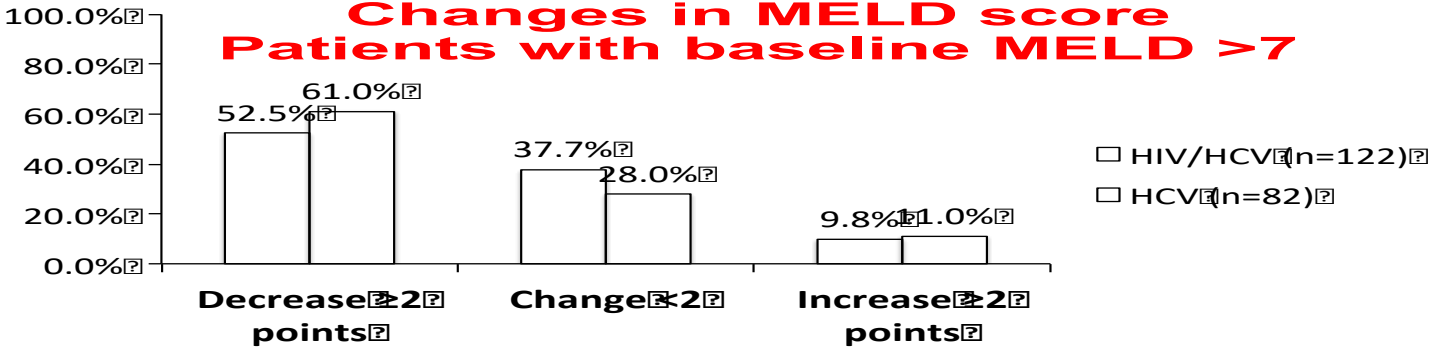
Frequency of worsening liver function by HIV status
Increase in CPT ≥1 point and/or MELD ≥ 2 points



Changes in CPT score
Patients with baseline CPT >5



Changes in MELD score
Patients with baseline MELD >7



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DAA response in HIV/HCV – take home messages

- Responses similar to HIV-neg, best responses BEFORE cirrhosis and significant portal hypertension
- Most cirrhotics including de-compensated cirrhotics will derive benefit from HCV clearance, HIV has no negative impact
- Maintain surveillance for HCC even after SVR12 achieved

Substantial decline in Acute HCV post DAA rollout in the Netherlands

(Rjinders, et al O137LB)

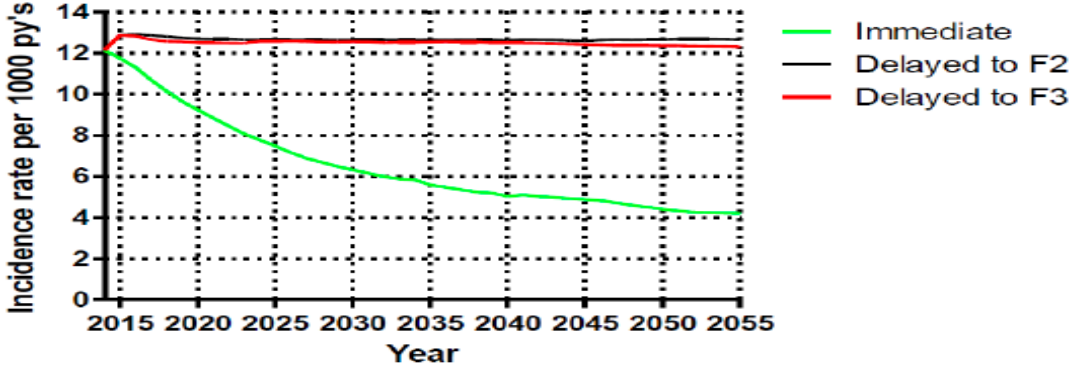
In 2014:

Nationwide incidence estimate from 19 HIV centers (80% of HIV+MSM in care)

99 A-HCV in 8849 PYFU => 11/1000 PYFU or 1.1% per year

Hullegie SJ et al Clin Microbiol Infect. 2016

⟹ Immediate DAA treatment is a cost-effective HCV prevention approach that can strongly reduce, but not eliminate, the HCV epidemic among HIV-infected MSM.



Substantial decline in Acute HCV post DAA rollout in the Netherlands

(Rjinders, et al O137LB)

Study hypothesis:

Unrestricted DAA access will result in a decrease in the number of new HCV infections in HIV+MSM

- By 2017, 742/971 (76%) HIV+ MSM patients treated for HCV
  - 50% 2014, 65% 2016, treated Acute HCV in the early phase via clinical trials (DAHHS 1 and 2 studies)

Substantial decline in Acute HCV post DAA rollout in the Netherlands

(Rjinders, et al O137LB)

2014

A-HCV **n = 93**

PYFU n = 8290

11.2/1000 PYFU (95% CI 9-14)

1.1% per year

2016

A-HCV **n = 49**

PYFU n = 8961

5.5/1000 PYFU (95% CI 4–7)

0,55% per year

IRR 0.49 (95% CI 0.34 – 0.69)

Jan-Dec 2014 11.2/1000

Jan-Jun 2016 6.9/1000

July-Dec 2016 4.0/1000

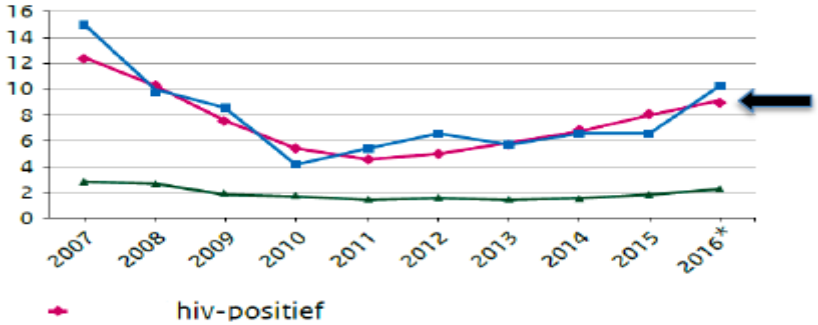
Decline NOT associated with reduction in risk-behaviour

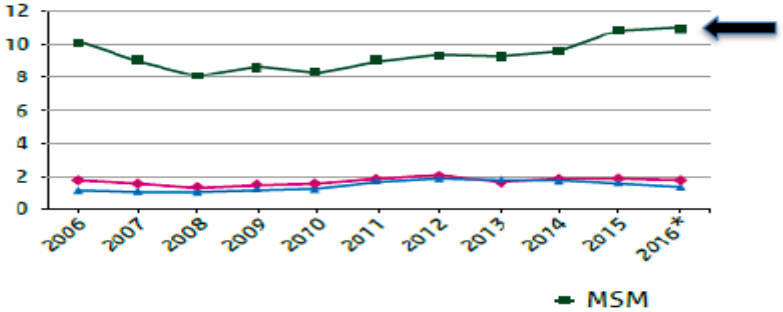
What about syphilis in MSM at public health STD clinics:

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





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BUT…HCV re-infections in GECCO

(Ingiliz et al, P567)

	GECCO population n=1,483
Median Age [years (IQR)]	54 (46-61)
Male [n (%)]	935 (63)
Mode of HCV transmission - IVDU [n (%)] - MSM [n (%)] - Other [n (%)]	 454 (31) 166 (11) 864 (58)
HIV coinfection [n (%)]	299 (21)
HCV genotype - GT 1 [n (%)] - GT 2 [n (%)] - GT 3 [n (%)] - GT 4 [n (%)]	 1,073 (72) 49 (3) 272 (18) 89 (6)

	Reinfection n=24
Median Age [years (IQR)]	49 (42-54.5)
Male [n (%)]	24 (100)
Mode of HCV transmission - IVDU [n (%)] - MSM [n (%)] - MSM + IVDU [n (%)]	 5 (21) 14 (58) 5 (21)
HIV coinfection [n (%)]	20 (83)
Median time to reinfection [weeks (IQR)]	41 (25-67)
Previous HCV treatment - SOF-PEG-RBV [n (%)] - SOF/LDV [n (%)] - PTV/r/OBV+/-DSV+/-RBV - SOF/RBV - SOF-DCV - SIM-SOF	 7 (29) 11 (46) 2 (9) 1 (5) 2 (9) 1 (5)

11% reinfection in MSM

1% reinfection in IVDU

Similar re-infection rates as in Pre-DAA era

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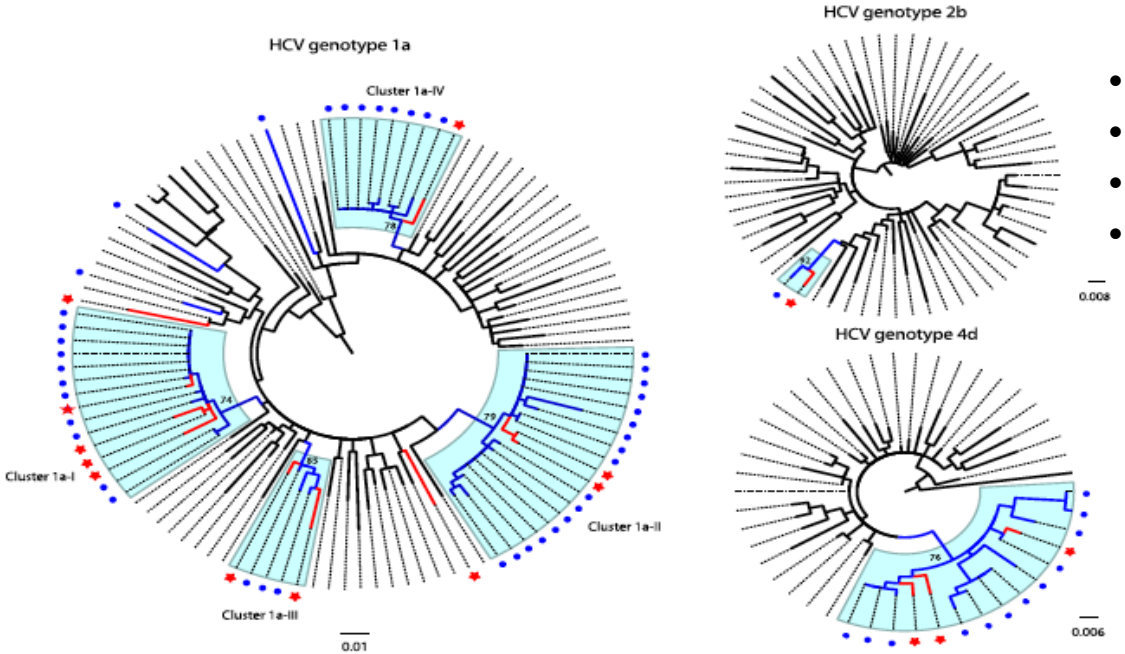
- So why might ‘TASP’ not work if we treated ALL/majority of HIV/HCV co-infected MSM patients?

- What might drive the difference in re-infection rates between countries?

High prevalence of HCV amongst HIV-neg MSM accessing PrEP – Amsterdam cohort

(Hoornenborg et al. P519)



- Pre-PrEP analysis
- 4.8% of 375 – HCV-infected
- Clustering of virus with HIV+ MSM
- Risk factors
  - Injecting Drug Use
  - Self-reported Chemsex
  - Condomless receptive anal sex

Figure 1: HCV NS5B fragment 2 phylogenetic trees for HCV subtypes 1a, 2b,and 4d comparing HCV sequences from HIV-negative MSM starting PrEP (red branches, red stars) with HCV sequences obtained from HIV-positive MSM (blue branches, blue dots) and unrelated HCV-positive people other than MSM (black branches) in the Netherlands.

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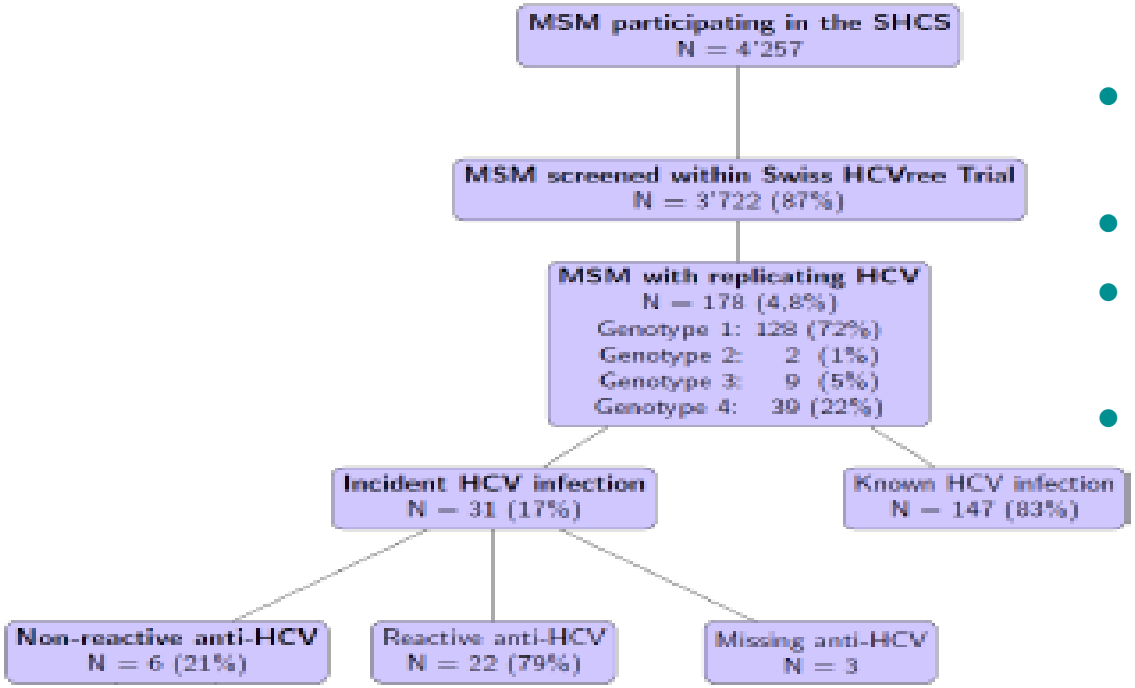
Swiss HIV Cohort – undiagnosed HCV

(Braun et al, P521)

Figure 1: Flow-chart of included MSM in the Swiss HCVree Trial



SHCS: Swiss HIV Cohort Study
MSM: men who have sex with men
HCV: hepatitis C virus infection
AST/ALT: aspartate aminotransferase/alanine aminotransferase

- Systematic screening with HCV RNA
- Dec 2015 – May 2016
- 17% previously undiagnosed
- 21% HCV-Ab negative at time of diagnosis

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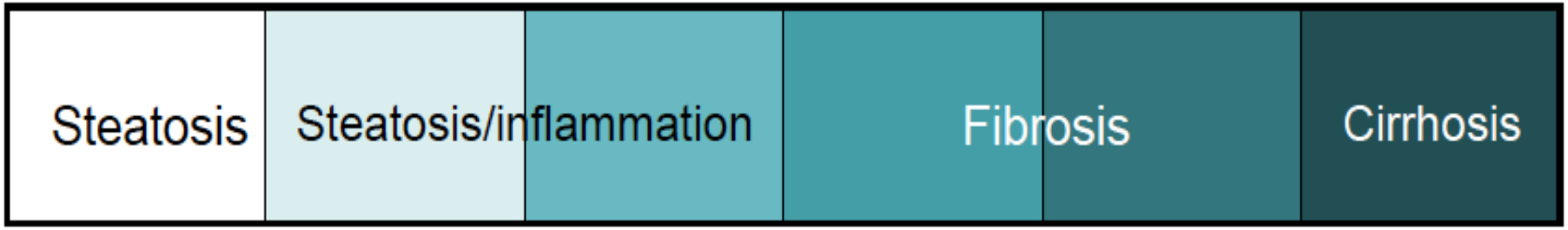
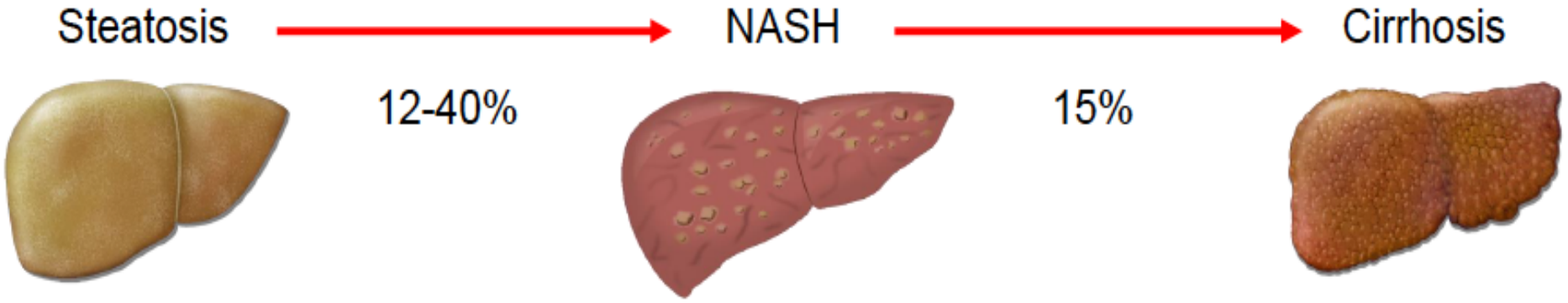
HCV – TaSP – take home messages

- Will only work if
  - High numbers of chronic HCV treated
  - High numbers of Acute HCV treated early (including re-infections)
  - High rates of diagnoses for early HCV, re-infections, and undiagnosed HCV in HIV+ and HIV-neg MSM
    - (?deleterious effect of risk compensation for HIV-PrEP – rate of new HCV incidence in IPERGAY – 18.5/1000 PYFU[1])
  - Combination Prevention (Active case-finding, early treatment and risk-behaviour modification)

1. Molina, et al, NEJM 2015; 373: 2237

Non-Alcoholic Fatty Liver Disease (NAFLD) – understanding the concepts





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Liver fibrosis and steatosis in HIV mono-infected patients – ECHAM (Lemoine, et al P703)

	n= 402
Age (year), median (IQR)	55 (50 – 61)
Male, n (%)	340 (85%)
BMI, kg/m^2 , median (IQR) Overweight (BMI >25 <30 kg/m^2) Obesity (BMI≥30 kg/m^2)	25.9 (23.6 – 28.7) 171 (42.5%) 71 (17.7%)
Elevated BP (Systolic > 140 and/or diastolic >90) and/or treated HBP	265 (66%)
Hyperglycaemia (≥ 5.6 mmol/L) and/or anti-diabetic treatment, n (%)	193 (48%)
Hypertriglyceridemia and/or treatment for hypertriglyceridemia n(%)	248 (62%)
Low HDL and/or treatment for hypercholesterolemia, n (%)	253 (63%)
Date of HIV diagnosis (years), median (IQR)	1995 (1991 – 2001)
Time on ART (years), median (IQR), n=387	16 (12 – 19)
CD4 nadir (cells/mm^3), median (IQR), n=371	184 (84 – 266)
HIV-RNA plasma viral load, median (IQR) Detectable plasma HIV-RNA, n(%)	<20 (<20 – <20) 11 (3%)
Current CD4 (cells/mm^3), median (IQR)	630 (510 – 832)
CD4/CD8 ratio, median (IQR)	0.86 (0.60 – 1.18)
AST (IU/L), median (IQR)	29 (23 – 37)
ALT (IU/L), median (IQR)	34 (24 – 50)
Elevated transaminases at inclusion, n	167 (41.5%)
GGT (IU/L), median (IQR)	48 (29 – 81)
Platelets (10^9 cells/L), median (IQR)	213 (178 – 253)
HOMA, median (IQR)	2.69 (1.74 – 4.64)
HOMA ≥ 2.5, n (%)	218 (54%)

Table 1. General characteristics of the study population

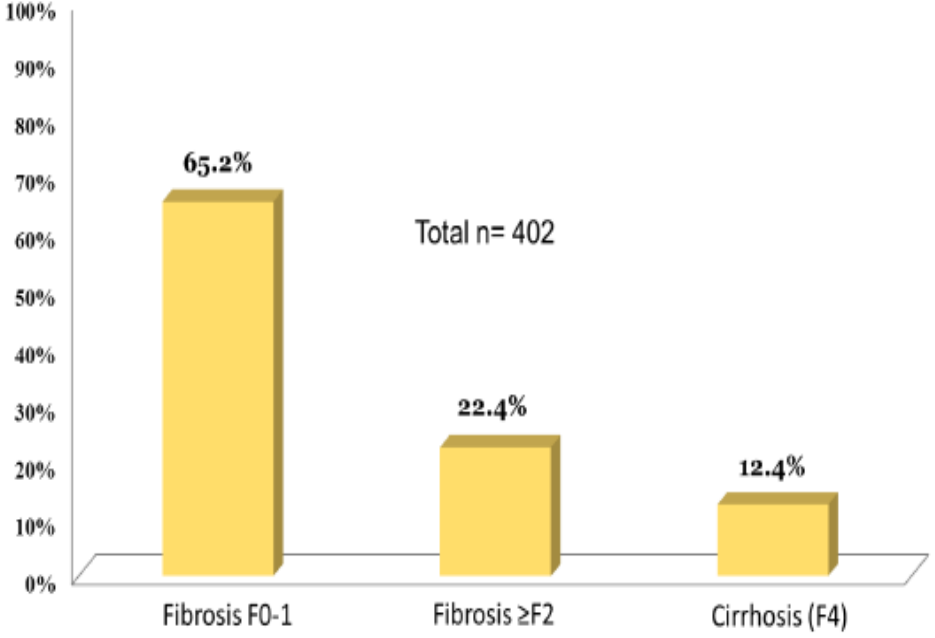

Figure 1. Proportion of patients with significant fibrosis and cirrhosis based on Fibroscan® and/or Fibrotest®

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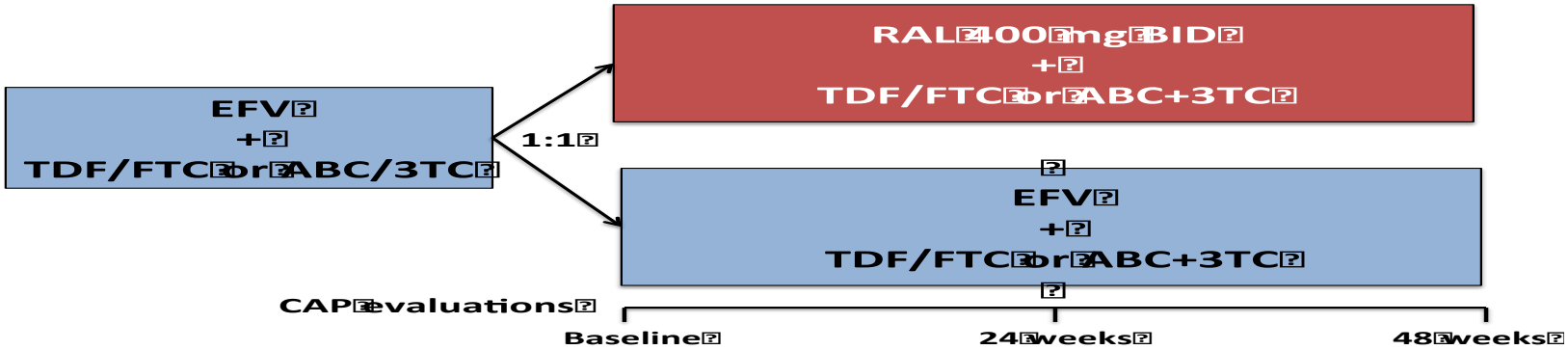
Switch from EFV to Raltegravir – beneficial effect on hepatic fat – STERAL study

(Macias et al, P697)

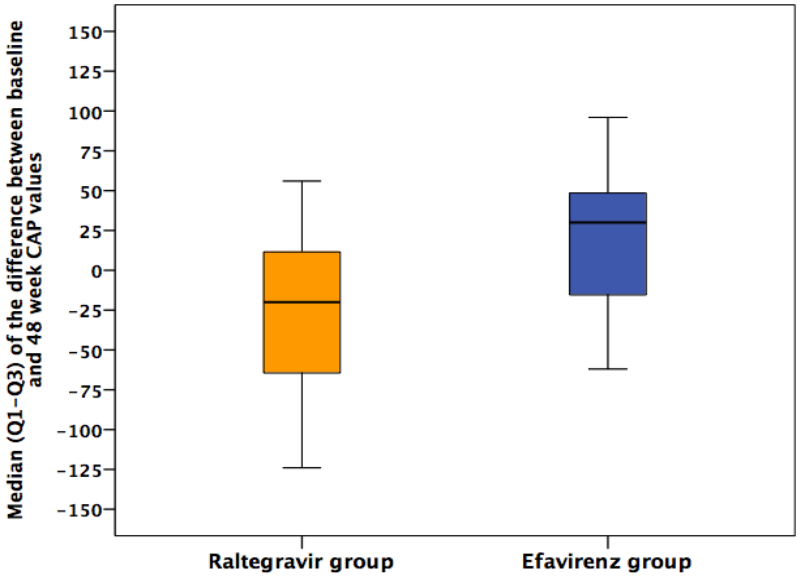
Randomized, controlled, open label, phase 4 clinical trial

- CAP ≥238 dB/m, indicative of steatosis involving >10% of hepatocytes.
- Daily alcohol intake <50 g for men and <40 g for women.
- Plasma HIV RNA <50 copies/ml for ≥24 weeks in, at least, two visits.

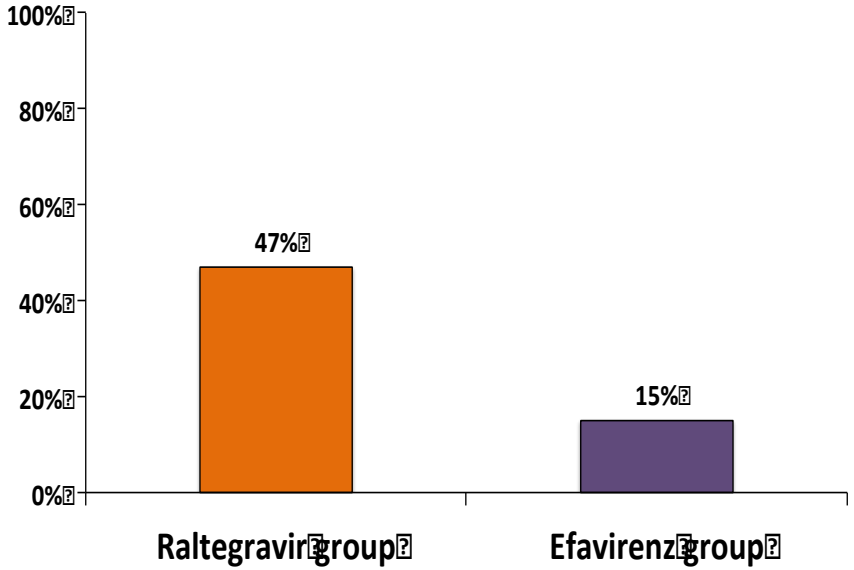


STERAL - results

Comparison of median changes in CAP values between baseline and week 48



Proportion of patients without significant steatosis (CAP <238 dB/m) at week 48



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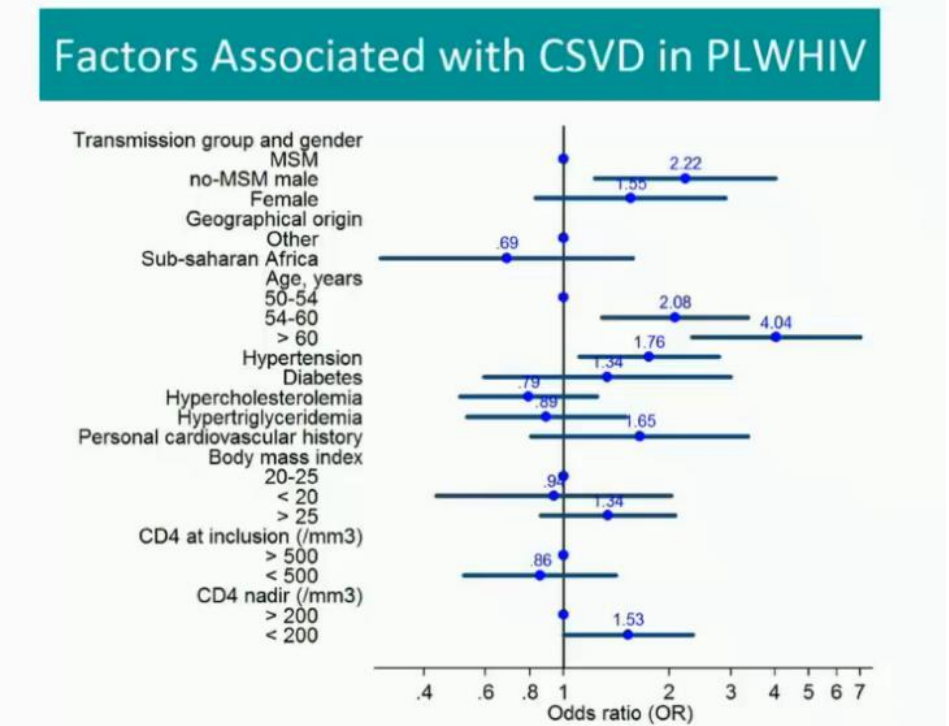
NAFLD – take home messages

- NAFLD increasingly recognised in HIV+ patients
- NAFL (hepatic steatosis) ≠ NASH (steatohepatitis)
- Natural history of NASH and fibrosis progression in HIV+ not well understood
  - Higher prevalence of NASH/Fibrosis amongst HIV+ NAFLD?
  - Faster fibrosis progression?
- HIV replication/ARVs and ARV classes may have a role

Cerebral small vessel disease in HIV-infected patients well controlled on cART – Microbreak 1 (Costagliola et al O75)

- Most long term HIV infection
  - Mostly male, median CD4 600
- MRI detected CSVD
  - ?clinical consequences
- Prevalence 52%
- Adj OR 2.3
  - vs HIV negative controls
- RF: age, HTN, CD4 nadir <200
- Impact of HIV less with increasing age (>60)



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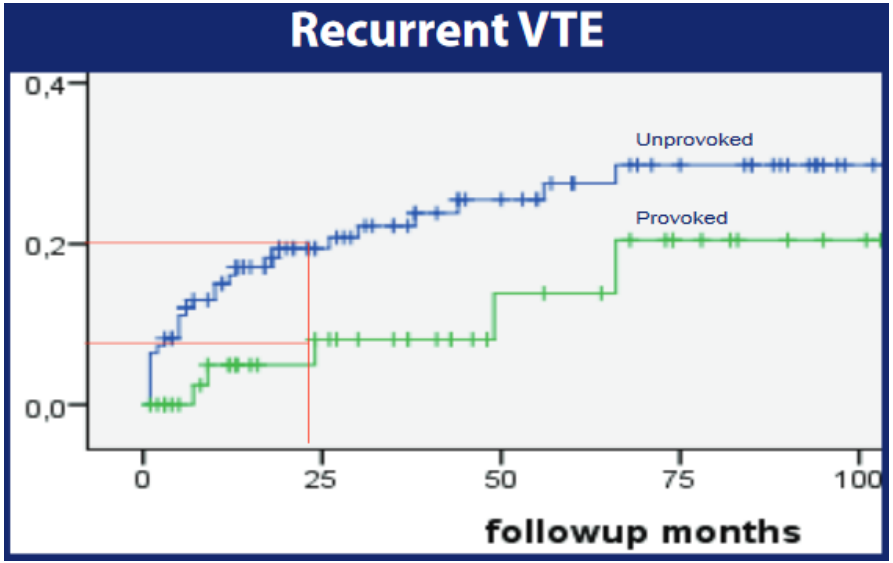
First and recurrent venous thrombosis in HIV patients of the Dutch ATHENA cohort (Rokx et al P620)

- Observational
- Virologically suppressed
- VTE incidence 2.3/1000PYFU

HIV Related VTE Risk Factors

		Hazard Ratio	(95%CI)	Incidence
HIV risk factors				
HIV-RNA	<100.000	1		
	>100.000	1.7	(1.1-2.8)	
CDC-C event		2.6	(1.6-4.1)	
CD4	<200	1		7.1 / 1000py
	200-350	0.8	(0.5-1.3)	3.2 / 1000py
	350-500	0.6	(0.4-1.0)	2.0 / 1000py
	>500	0.4	(0.3-0.7)	1.3 / 1000py

- No assoc with ART

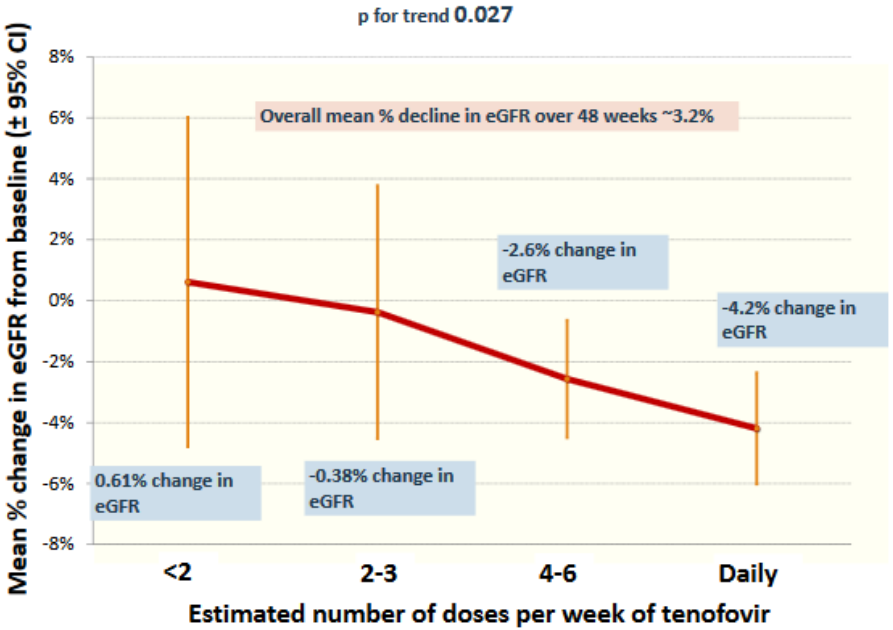


Recurrence rate high in 'unprovoked'
• esp first yr after anticoag stopped

Take home: if unprovoked VTE and low CD4 ?longer anticoagulation

Older Age Associated with both Adherence and Renal Decline in the PrEP Demo Project (Gandhi et al P978)

- Predictors of eGFR decline on PrEP
  - Age
  - Higher baseline eGFR
  - Higher concentration of PrEP drug
- Predictors of eGFR falling below 70
  - Lower eGFR at baseline
  - Age >45
- **Take home: Older MSM are more adherent to PrEP but may need more frequent monitoring**



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Frailty progression and recovery among persons aging with HIV and substance use

ALIVE (Piggott et al O133)

Virologic Suppression and Early HIV Control Reduces Frailty Progression

	FRAILTY PROGRESSION	
	Nonfrail -> Frail Adj OR (95% CI)	Robust -> Frail Adj OR (95% CI)
MODEL A:		
HIV+, viremic	Ref	Ref
HIV+, suppressed (VL<50)	0.74 (0.58, 0.95)	0.69 (0.52, 0.92)
HIV negative	0.71 (0.59, 0.85)	0.62 (0.49, 0.77)
MODEL B:		
HIV+, prior AIDS	Ref	Ref
HIV+, no AIDS	0.67 (0.51, 0.88)	0.61 (0.43, 0.85)
HIV negative	0.60 (0.46, 0.77)	0.50 (0.37, 0.68)
MODEL C:		
HIV+, nadir<50	Ref	Ref
HIV+, nadir 50-200	1.24 (0.90, 1.71)	1.04 (0.71, 1.51)
HIV+, nadir 200-350	1.10 (0.77, 1.58)	0.86 (0.57, 1.30)
HIV+, nadir 350-500	1.51 (0.94, 2.43)	1.11 (0.63, 1.95)
HIV+, nadir >500	0.42 (0.16, 1.11)	0.31 (0.11, 0.90)
HIV negative	0.93 (0.70, 1.23)	0.71 (0.51, 0.98)

- Inflammation assoc woth frailty
- Frailty scores can improve
  - HIV VL suppression
  - CD4>500
  - No prior AIDS diagnosis

• Take home: giving early consistent ART, reducing chronic inflammation, attain viral suppression can improve frailty to match HIV neg population

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BHIVA ‘Best of CROI’ Working Party 2017

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Dr David Chadwick
Dr Duncan Churchill
Mr Simon Collins
Dr Alessia Dalla Pria
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