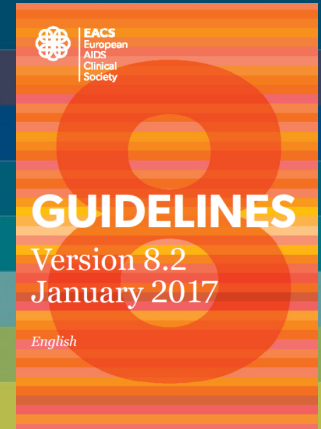


HIV/hepatitis co-infection

Christoph Boesecke
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University Hospital Bonn
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EACS European
AIDS Clinical Society



Clinical Management and Treatment of HBV and HCV Co-infection in HIV- positive Persons

Assessment of HIV-positive Persons at Initial & Subsequent Visits

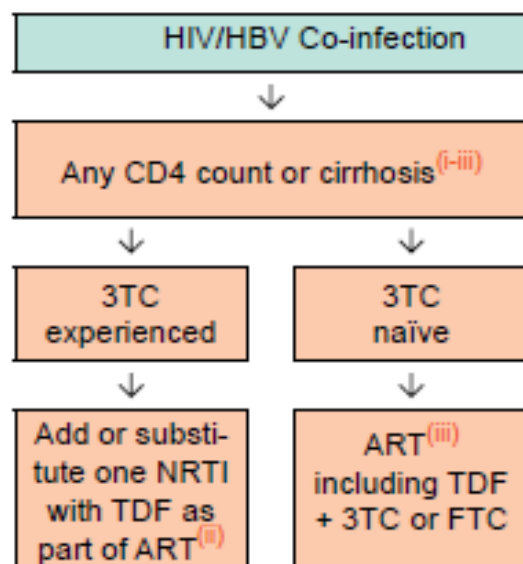
	Assessment	At HIV diagnosis	Prior to starting ART	Follow-up frequency	Comment
Viral Hepatitis	HAV serology	+		Annual/ as indicated	Screen at risk; vaccinate if non-immune
	HCV screen	+			Annual screen if ongoing risk Measure HCV-RNA if HCV Ab pos or if acute infection suspected
	HBV screen	+	+		Annual screen in susceptible persons; vaccinate if non-immune



Hepatitis B Co-infection



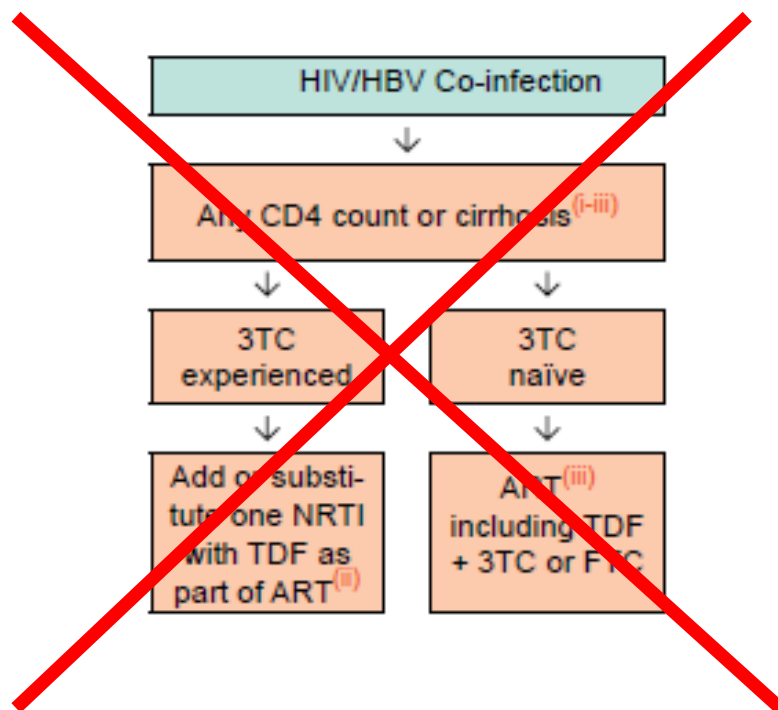
Treatment of Chronic HBV in Persons with HBV/HIV Co-infection



- i For management of cirrhotic persons, see pages 51-54. Persons with liver cirrhosis and low CD4 count require careful surveillance in the first months after starting ART in order not to overlook immune reconstitution syndrome and subsequent liver decompensation due to flares of liver enzymes.
- ii All persons with HBV/HIV co-infection should receive ART including TDF (or TAF) + 3TC or FTC unless history of TDF intolerance. In HBV/HIV co-infected persons with bone mineral density changes or chronic kidney disease, see recommendations for [Dose Adjustment of ARVs for Impaired Renal Function](#) and page 47. If TDF or TAF is strictly contraindicated, entecavir + adefovir may be tried. However, efficacy and renal toxicity need to be closely monitored, because of the proven renal toxicity of adefovir. In persons with no prior 3TC exposure, entecavir may be used alone. NRTI substitution should only be performed if feasible and appropriate from the perspective of maintaining HIV suppression. Caution is warranted to switch from a TDF-based regimen to drugs with a lower genetic barrier, e.g. FTC or 3TC, in particular in 3TC-pretreated cirrhotic persons as viral breakthrough due to archived YMDD mutations is likely to happen. This has also been described in individuals with previous 3TC HBV-resistance who have been switched from TDF to entecavir. The addition of entecavir to TDF in persons with low persistent HBV-replication has not statistically proved to be efficient and should therefore be avoided. Results of trials are awaited.
- iii The optimal treatment duration for nucleos(t)ide analogues with anti-HBV activity has not yet been determined and experts recommend life-long therapy if anti-HBV nucleos(t)ides are given as part of ART. In those on ART where the nucleoside backbone needs changing, anti-HBV therapy may be stopped cautiously in HBeAg positive persons who have achieved HBe-seroconversion for at least six months or after confirmed HBs-seroconversion in those who are HBeAg negative. In persons with liver cirrhosis, stopping of effective anti-HBV treatment is not recommended in order to avoid liver decompensation due to flares of liver enzymes.



Treatment of Chronic HBV in Persons with HBV/HIV Co-infection



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- ii All persons with HBV/HIV co-infection should receive ART including TDF (or TAF) + 3TC or FTC unless history of TDF intolerance. In HBV/HIV co-infected persons with bone mineral density changes or chronic kidney disease, see recommendations for [Dose Adjustment of ARVs for Impaired Renal Function](#) and page 47. If TDF or TAF is strictly contraindicated, entecavir + adefovir may be tried. However, efficacy and renal toxicity need to be closely monitored, because of the proven renal toxicity of adefovir. In persons with no prior 3TC exposure, entecavir may be used alone. NRTI substitution should only be performed if feasible and appropriate from the perspective of maintaining HIV suppression. Caution is warranted to switch from a TDF-based regimen to drugs with a lower genetic barrier, e.g. FTC or 3TC, in particular in 3TC-pretreated cirrhotic persons as viral breakthrough due to archived YMDD mutations is likely to happen. This has also been described in individuals with previous 3TC HBV-resistance who have been switched from TDF to entecavir. The addition of entecavir to TDF in persons with low persistent HBV-replication has not statistically proved to be efficient and should therefore be avoided. Results of trials are awaited.
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So far, so boring.

Any HBV/HIV news?

THE place to go for exciting news:



THE place to go for exciting news:



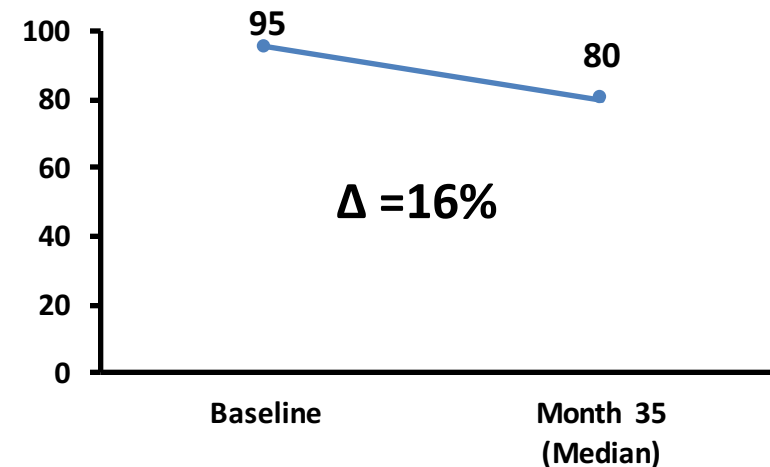
HBV Seroconversion More Frequent in HIV Coinfection

- 2 German Centres

Baseline and FU Parameters

N=95	
Median Age [Years] (IQR)	40 (34-45)
Male Sex [%]	78
Main HIV Transmission Risks [MSM/HP/Het; %]	43/24/12
CDC C3 [%]	25
TDF and/or 3TC as 1 st Line Art [%]	43
Median CD4 T cells [/ul] (IQR)	270 (140-480)
Median Follow-up [Months] (IQR)	107 (76-144)
Median CD4 T Cell Gain [/ul] (IQR)	165 (3-315)
Median Time to HBsAg Loss [Months] (IQR)	35 (18-49)

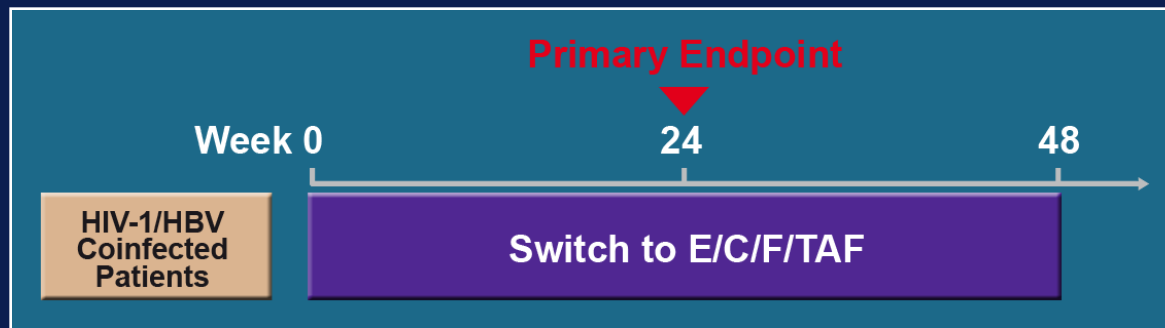
HBsAg Loss



- ▶ HBsAg-loss in 16% (15/95)
- ▶ Anti-HBs in 80% (12/15)
- ▶ Anti-HBe in 27% (26/95)

Switching from TDF to TAF in HBV/HIV coinfection

- Phase 3b open label in Japan and North America
- 72 patients (96% on TDF)
- Switch from any cART to E/C/F/TAF
- HBsAg+, no cirrhosis, eGFR >50mL/min



⇒ No influence on HIV-RNA and HBV-DNA

⇒ No change in eGFR

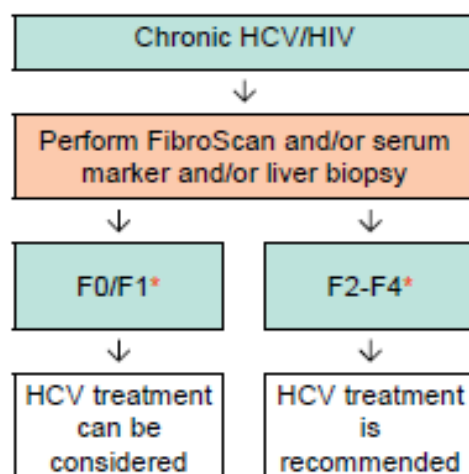
2 notes of caution

- TDF or TAF provide protection against HBV in vaccine non-responders
- Consider addition of TDF or TAF in HIV-patients with full HBV seroconversion and no HBV-active cART undergoing chemotherapy/immunosuppression

Hepatitis C Co-infection



Management of Persons with Chronic HCV/HIV Co-infection



- * Metavir fibrosis score: F0=no fibrosis; F1=portal fibrosis, no septae; F2=portal fibrosis, few septae; F3=bridging fibrosis; F4=cirrhosis.
FibroScan®: F0-F1 < 7.1 kPa; F2 7-10 kPa; F3/F4 > 10 kPa
Treatment must be considered independently from liver fibrosis in persons with low CD4 count (< 200 cells/ μ L), ongoing HIV replication, HBV co-infection, debilitating fatigue, extrahepatic manifestations, high risk of HCV transmission (IVDU, prisoners, MSM with high risk behavior, fertile women who want to be pregnant).



HCV Treatment Options in HCV/HIV Co-infected Persons

IFN-free HCV Treatment Options				
HCV GT	Treatment regimen	Treatment duration & ribavirin usage		
		Non-cirrhotic	Compensated cirrhotic	Decompensated cirrhotics CTP class B/C
1 & 4	SOF + SMP +/- RBV	GT 4 only: 12 weeks with RBV or 24 weeks without RBV ⁽ⁱ⁾		Not recommended
	SOF/LDV +/- RBV	8 weeks without RBV ⁽ⁱⁱ⁾ or 12 weeks +/- RBV ⁽ⁱⁱⁱ⁾	12 weeks +/- RBV or 24 weeks without RBV ^(iv)	
	SOF + DCV +/- RBV	12 weeks +/- RBV ⁽ⁱⁱⁱ⁾	12 weeks +/- RBV or 24 weeks without RBV ^(iv)	
	SOF + VEL	12 weeks		12 weeks with RBV
	OBV/PTV/r + DSV	8 ^(v) -12 weeks in GT 1b	12 weeks in GT 1b	Not recommended
	OBV/PTV/r + DSV + RBV	12 weeks in GT 1a	24 weeks in GT 1a	Not recommended
	OBV/PTV/r + RBV	12 weeks in GT 4		Not recommended
	EBR + GZR	12 weeks ^(vi)		Not recommended
2	SOF + DCV	12 weeks		12 weeks with RBV
	SOF + VEL	12 weeks		12 weeks with RBV
3	SOF + DCV +/- RBV	12 weeks +/- RBV ^(vi) or 24 weeks without RBV	24 weeks with RBV	
	SOF + VEL +/- RBV	12 weeks +/- RBV ^(vi) or 24 weeks without RBV		24 weeks with RBV
5 & 6	SOF/LDV +/- RBV	12 weeks +/- RBV or 24 weeks without RBV ⁽ⁱ⁾	12 weeks with RBV or 24 weeks without RBV ⁽ⁱ⁾	12 weeks with RBV or 24 weeks without RBV
	SOF + DCV +/- RBV	12 weeks +/- RBV or 24 weeks without RBV ⁽ⁱ⁾	12 weeks with RBV or 24 weeks without RBV ⁽ⁱ⁾	12 weeks with RBV or 24 weeks without RBV
	SOF + VEL	12 weeks		12 weeks with RBV

DCV = daclatasvir

DSV = dasabuvir

EBR = elbasvir

GZR = grazoprevir

LDV = ledipasvir

OBV = ombitasvir

PTV/r = paritaprevir/RTV

RBV = ribavirin

SMP = simeprevir

SOF = sofosbuvir

VEL = velpatasvir

RAS = Resistance Associated Substitutions

i In treatment experienced persons RBV treatment for 12 weeks or prolong treatment to 24 weeks without RBV

ii 8 weeks treatment without RBV only in treatment-naïve persons with F < 3 and baseline HCV-RNA < 6 million IU/mL

iii Addition of RBV in GT1a treatment experienced persons, but not in persons without NS5A RASs, if RASs testing is available

iv RBV can be avoided in GT1b, GT4 treatment-naïve, GT1a treatment-naïve and in GT1a experienced persons without NS5A RASs, if RASs testing is available; in persons intolerant to RBV, treatment may be prolonged to 24 weeks

v 8 weeks treatment without RBV only in persons without cirrhosis

vi Extension of treatment to 16 weeks and addition of RBV in persons with GT1a with baseline HCV-RNA > 800,000 IU/mL and NS5A RASs and in HCV GT4 experienced persons with HCV-RNA > 800,000 IU/mL

vii Addition of RBV only in treatment experienced persons with baseline NS5A RASs, if RAS testing available; if these persons are intolerant to RBV treatment may be prolonged to 24 weeks without RBV

Drug-drug Interactions between DAAs and ARVs

HCV drugs	ATV/r	DRV/c	DRV/r	LPV/r	EFV	ETV	NVP	RPV	MVC	DTG	EVG/c	RAL	ABC	FTC	3TC	TAF	TDF	ZDV
boceprevir	D35%	↓D	↓32% D44%	↓45% D34%	↓19% E20%	↑10% D23%	↓E	↓6% E39%	E	↔	↓D	↔	↔	↔	↔	D ⁱ	↔	↔
daclatasvir	↑110% ⁱⁱ	↑	↑41%	↑15%	↓32% ⁱⁱⁱ	↓	↓	↔	↔	E33%	↑ ^{iv}	↔	↔	↔	↔	↔	↑10% E10%	↔
elbasvir/ grazoprevir	↑	↑	↑	↑	↓54/83%	↓	↓	↔	↔	↔	↑	E43%	↔	↔	↔	E	↓7/14% E34%	↔
parita- previr/r/ ombitasvir/ dasabuvir	↑94% ^v	↑	D ^{vi}	↑	↔ ^{vii}	↓E?	↓E?	E ^{viii}	E	↔	↑	E134%	↔	↔	↔	E	↔	↔
parita- previr/r/ombi- tasvir	↑ ^{ix}	↑	↑ ^{ix}	↑	↔ ^{vii}	↓E?	↓E?	E ^{viii}	E	↔	↑	E20%	↔	↔	↔	E	↔	↔
simeprevir	↑	↑	↑	↑	↓71%	↓	↓	↑6% E12%	↔	↔	↑	↓11% E8%	↔	↔	↔	↔	↓14% E18%	↔
sofosbuvir/ ledipasvir	↑8/113% ^x	↑E ^x	↑34/ 39% ^{ix}	↔ ^x	↓34%	↔	↔	↔ ^x	E?	↔	↑36/ 78%E ^x	D≈20%	↔	↔	↔	E32%	E ^x	↔
sofosbuvir/ velpatasvir	↑/142% ^x	↔ ^{ix}	↓28%/- ^x	↓29%/- ^x	↓53%	↓	↓	↔	E?	↔	↔	↔	↔	↔	↔	↔	E ^x	↔
sofosbuvir	↔	↑	↑34%	↔	↓6% D4%	↔	↔	↑9% E6%	↔	↔	↔	↓5% D27%	↔	↓6%	↔	↔	↓6%	↔
telaprevir	↓20% E17%	↓D	↓35% D40%	↓54%	↓26% D7%	↓16%	↓?	↓5%E	E	E25%	↑13% D16%	E31%	↔	↔	↔	D ⁱ	E30% ^{ix}	↔

Legend

- ↑ potential elevated exposure of DAA
- ↓ potential decreased exposure of DAA
- ↔ no significant effect
- D potential decreased exposure of ARV drug
- E potential elevated exposure of ARV drug

Numbers refer to decreased/increased AUC of DAAs and ARVs as observed in drug interactions studies. Sofosbuvir/ledipasvir: first/second numbers refer to changes AUC sofosbuvir/ledipasvir.

- i Potential hematological toxicity
- ii Daclatasvir should be reduced to 30 mg qd with ATV/r or EVG/c.
No dose reduction with unboosted ATV
- iii Daclatasvir should be increased to 90 mg qd
- iv Use only with unboosted ATV and in persons without significant HIV PI mutations (ATV increased paritaprevir exposure due to CYP3A4 and OATP1B1/3 inhibition, not recommended without dasabuvir)
- v Co-administration decreased DRV trough concentration by approximately 50%. Although co-administration of DRV with ombitasvir/paritaprevir + dasabuvir is not recommended in the US Prescribing Information, the European SPC advises that DRV (dosed at 800 mg qd and administered at the same time as ombitasvir/paritaprevir + dasabuvir) can be used in the absence of extensive HIV PI resistance and should be taken without additional RTV
- vi Not recommended due to increase in paritaprevir exposure when co-administered with DRV 800 mg given with ombitasvir, paritaprevir, ritonavir (Viekirax). Of note: exposures of paritaprevir greater than this have been evaluated in phase 2 studies and were not expected to have a clinically meaningful impact on safety
- vii Severe tolerability issues
- viii Not recommended unless benefit outweighs the risk due to potential for QT interval prolongation with higher concentrations of rilpivirine, co-administration should only be considered in persons without known QT prolongation and without other QT prolongation co-medications
- ix Frequent monitoring of kidney function due to increase of TDF if contained in the regimen
- x The DAA can affect the intracellular activation of TAF

Colour legend

- no clinically significant interaction expected.
- these drugs should not be co-administered.
- potential interaction which may require a dosage adjustment or close monitoring.

Note: the symbol (green, amber, red) used to rank the clinical significance of the drug interaction is based on <http://www.hep-druginteractions.org>.

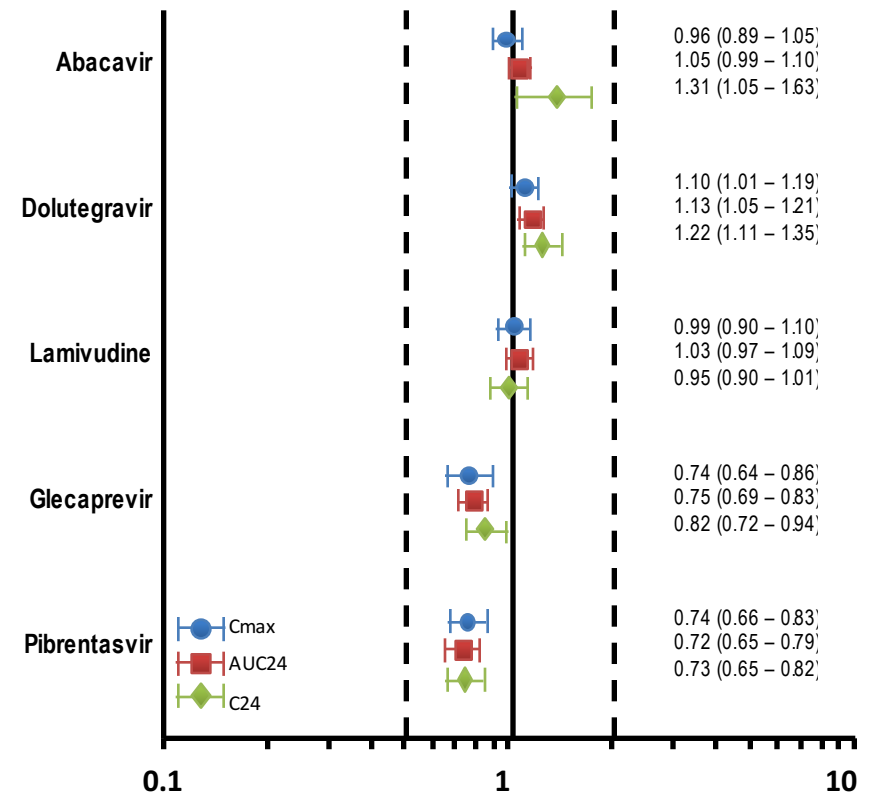
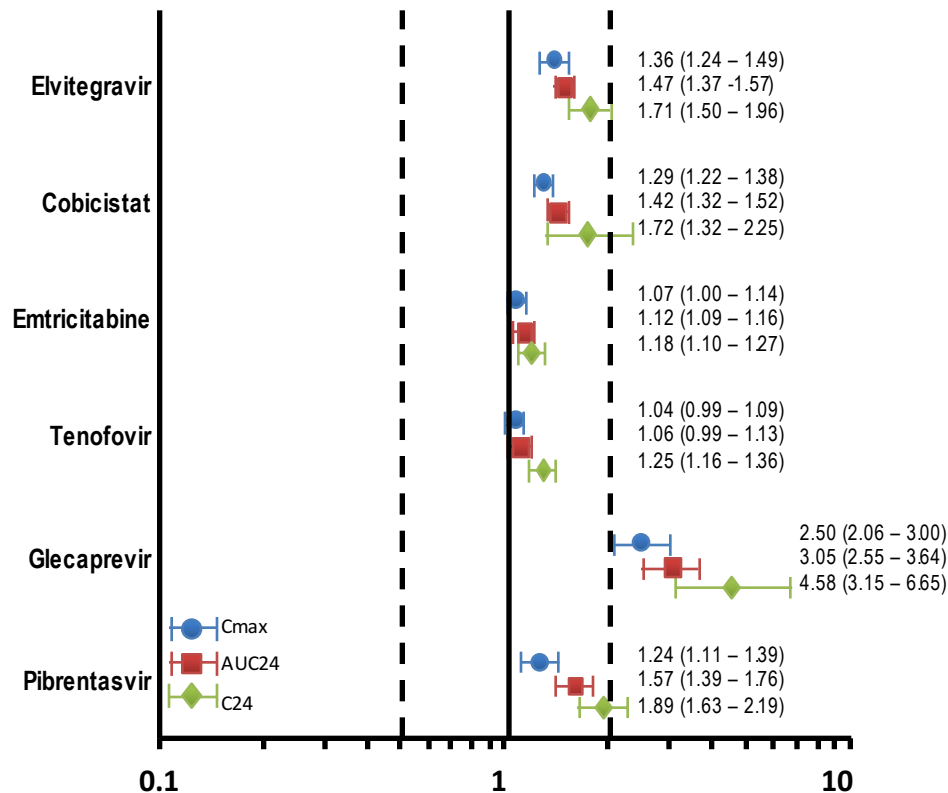


DDI: Glecaprevir & Pibrentasvir

- GT 1-6
- PK-data in 24 HIV- healthy volunteers

▲ GLE 300mg + PIB 120mg qd

▲ ART: Genvoya or Triumeq



No dose adaptation recommended

Recent HCV/HIV rumours

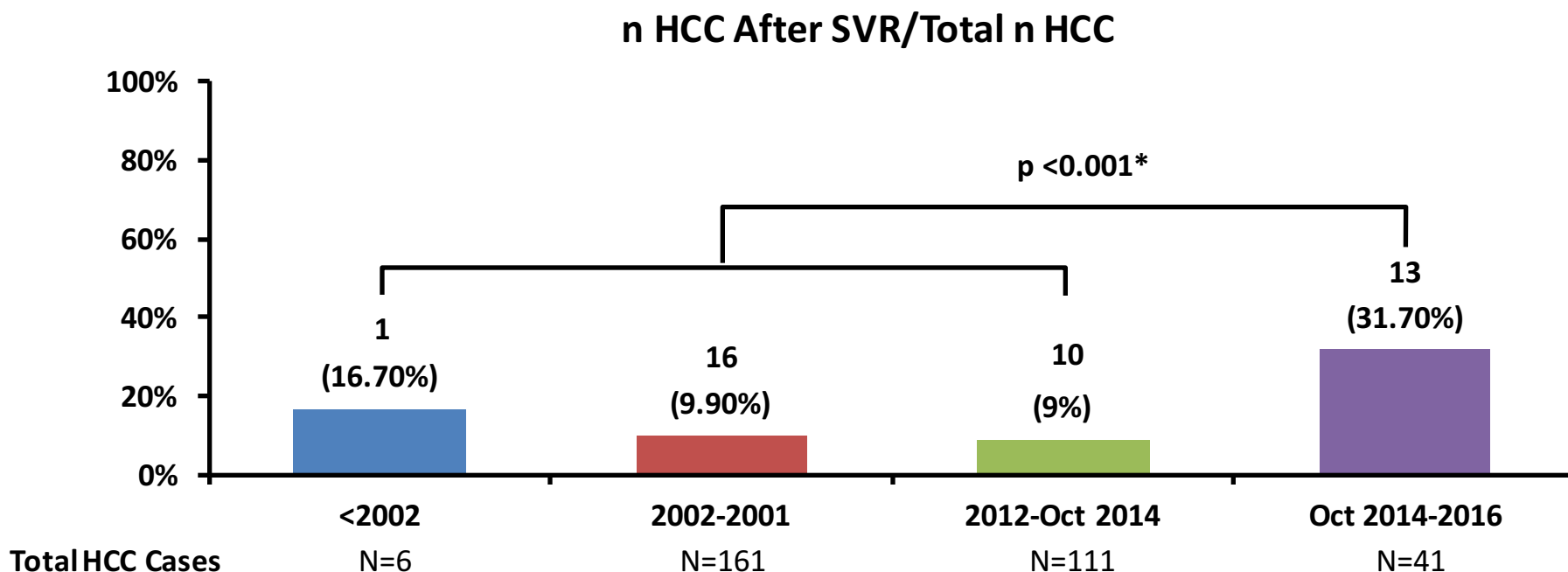
From the 2nd exciting place on earth:



- DAA cause HCC?
- Coinfection reduces SVR?

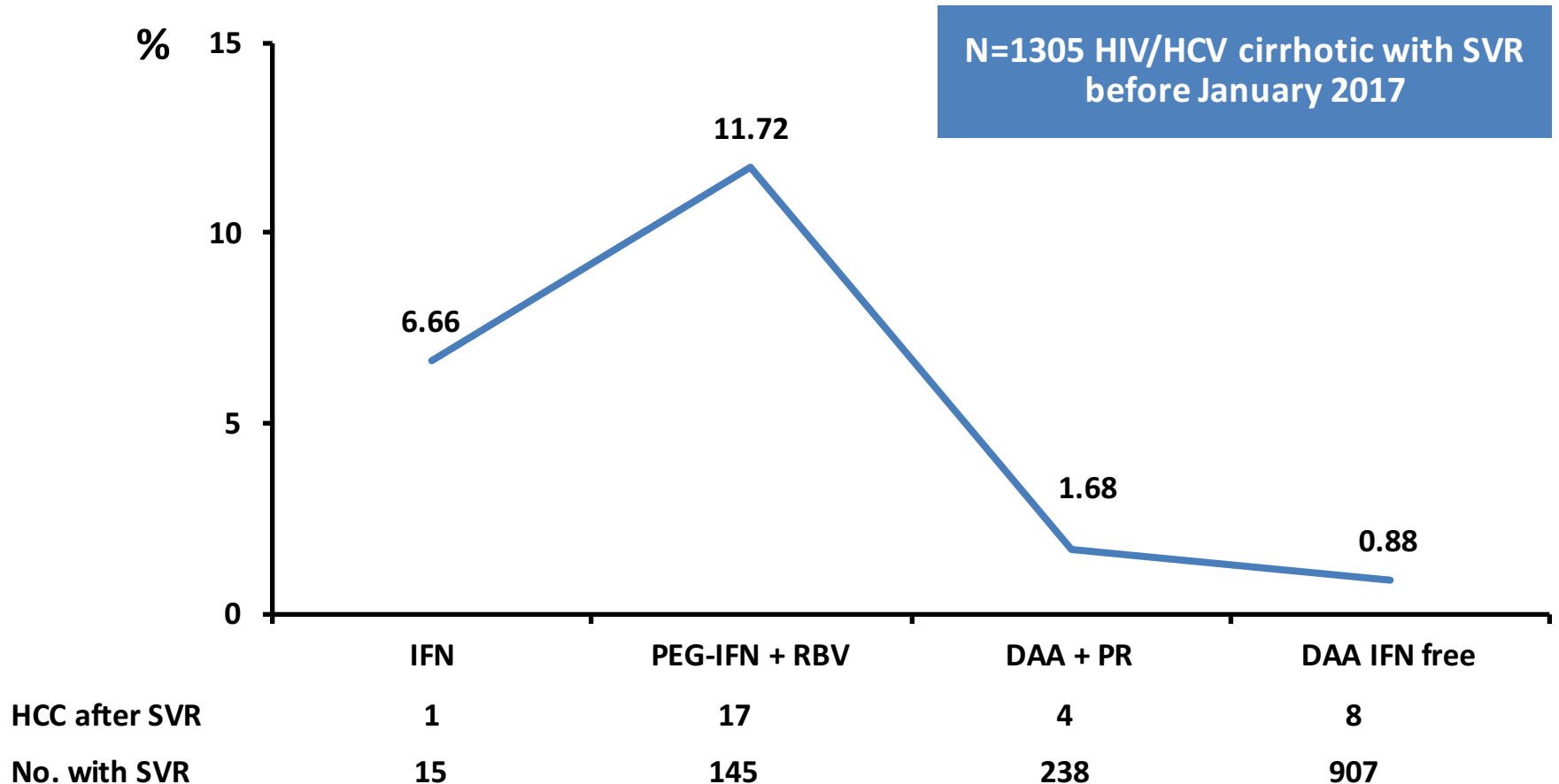
GEHEP 002 Spanish HCV/HIV Cohort: HCC after DAA therapy

- 319 HCV/HIV patients with HCC from 32 Spanish centres
- 45% pretreated
- HCC after median 16-24 months after SVR
- No increased HCC recurrence rate after SVR



Frequency of HCC Diagnosis After SVR in HIV/HCV Coinfected Patients with Cirrhosis

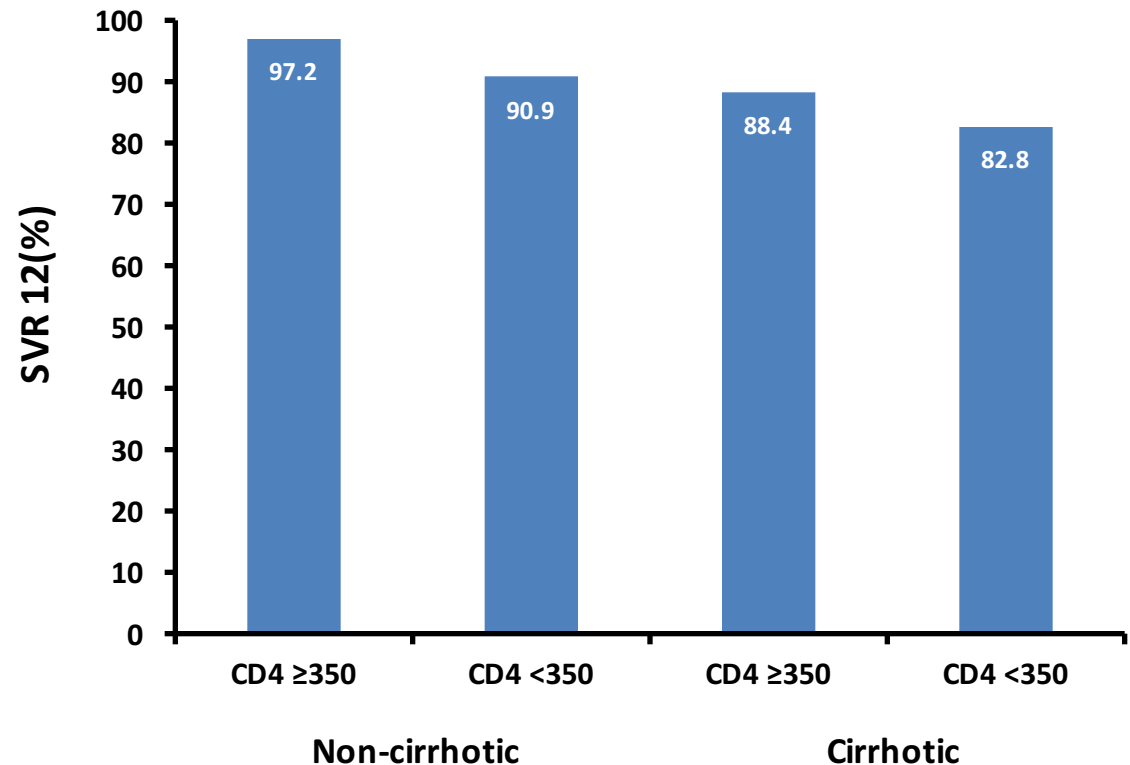
19 centers from the GEHEP-002 cohort reported data of the number of HIV/HCV-coinfected patients with cirrhosis who achieved SVR in each period



DAA Really Similarly Effective in HIV Coinfection?

SVR12 According to CD4 and Cirrhosis Status

- GECCO Cohort (9 German centres)
- n=1505
- 1156 mono-, 349 coinfectd
- Liver cirrhosis 29% (31% vs. 22%)
- Overall-SVR 95%, 95% monoinfected, 94% coinfectd



SVR lower in pts. with CD4 <350/ μ l and liver cirrhosis

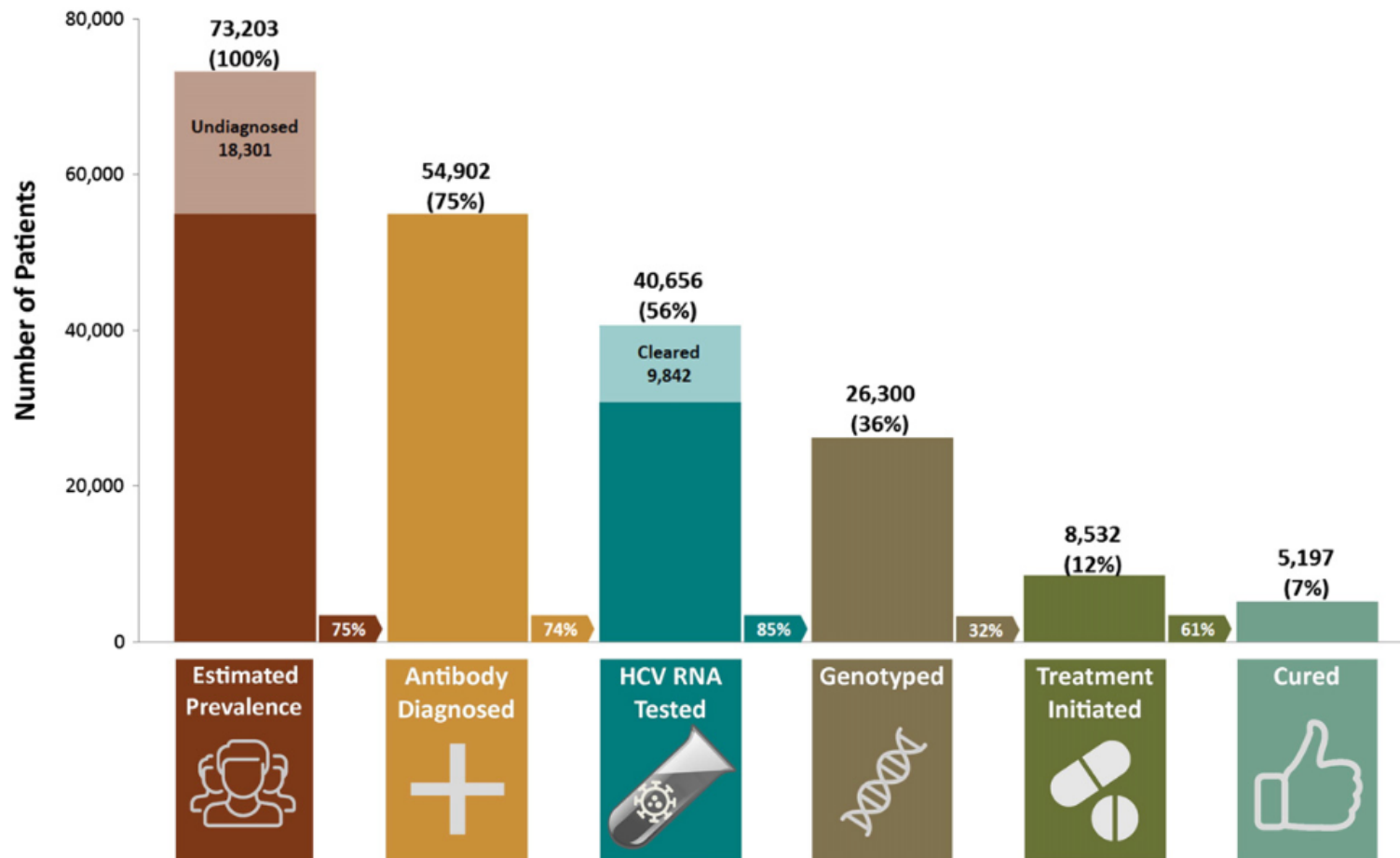
So, why do we still
(need to) talk about HCV?

The Population Level Cascade of Care for Hepatitis C in British Columbia, Canada: The BC Hepatitis Testers Cohort (BC-HTC)



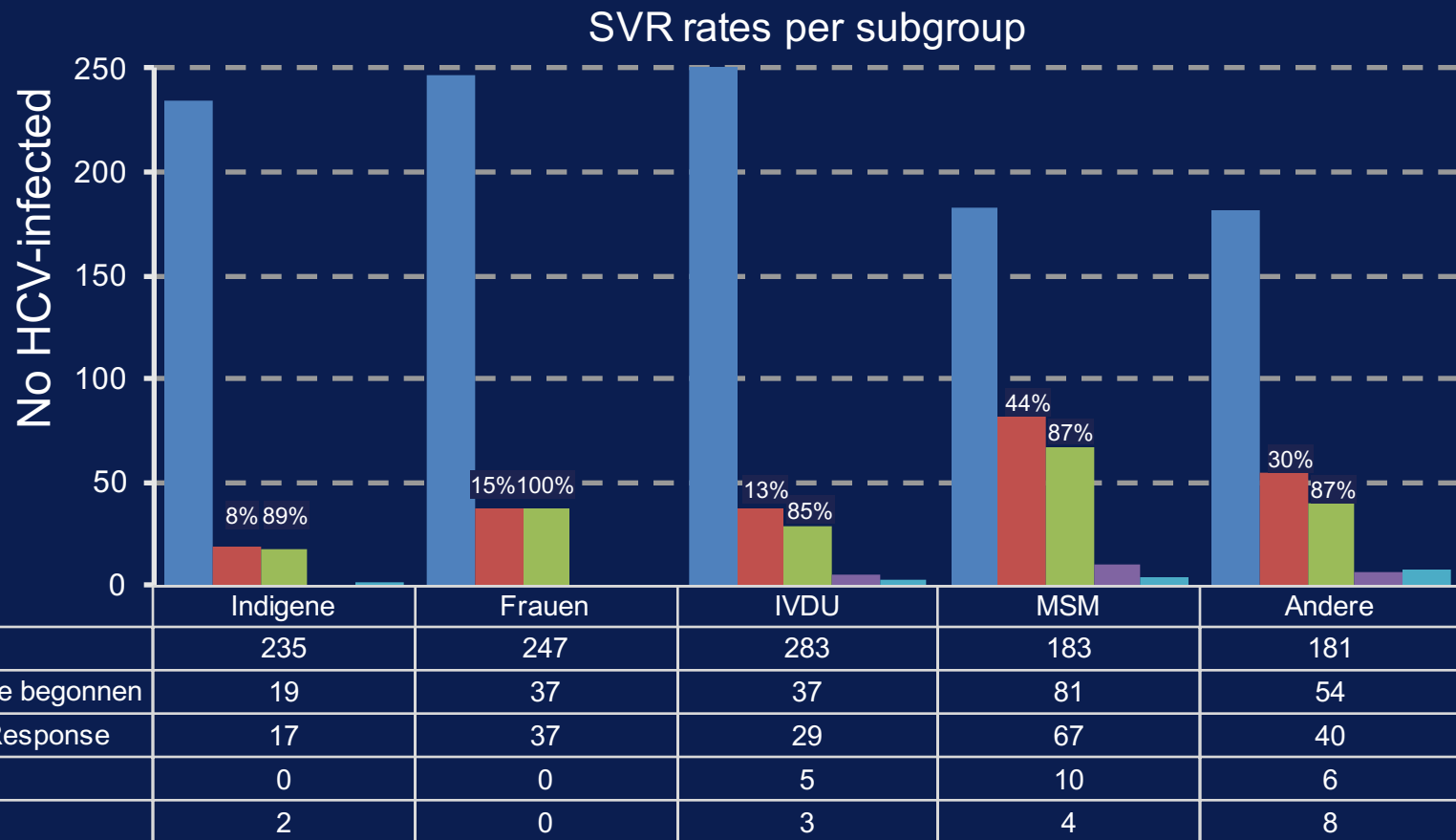
Naveed Z. Janjua DrPH^{a,b,*}, Margot Kuo MPH^a, Amanda Yu MSc^a, Maria Alvarez MSc^a, Stanley Wong MSc^a, Darrel Cook MSc^a, Jason Wong MD^{a,b}, Jason Grebely PhD^c, Zahid A. Butt PhD^{a,b}, Hasina Samji PhD^{a,b}, Alnoor Ramji MD^d, Mark Tyndall MD^{a,b}, Mel Krajden MD^{a,e}

N.Z. Janjua et al. / EBioMedicine 12 (2016) 189–195



Who receives DAA treatment?

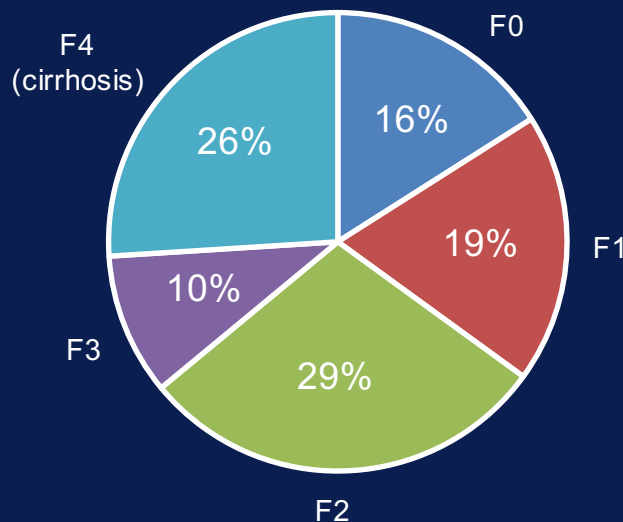
- 1.129 patients from the Canadian Coinfection Cohort
- 24% treated with DAA, SVR 91%



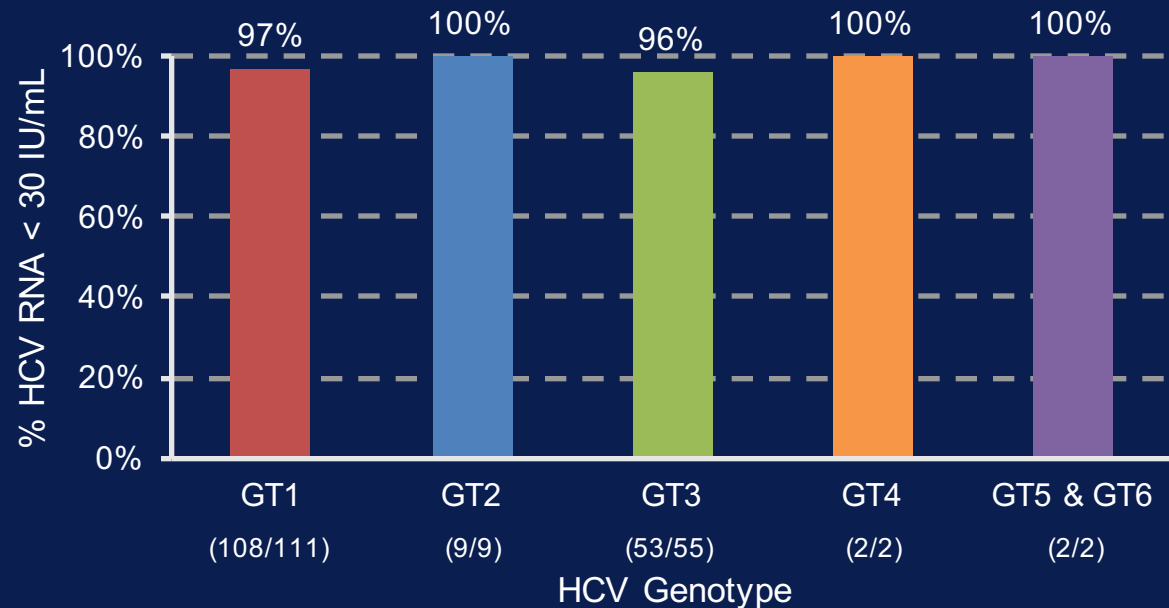
Buyers Clubs Worldwide

- 1150 HCV-patients
- SOF, DCV, LDV via Buyers Clubs in Australia, China, Russia, South-East-Asia

Baseline Fibrosis

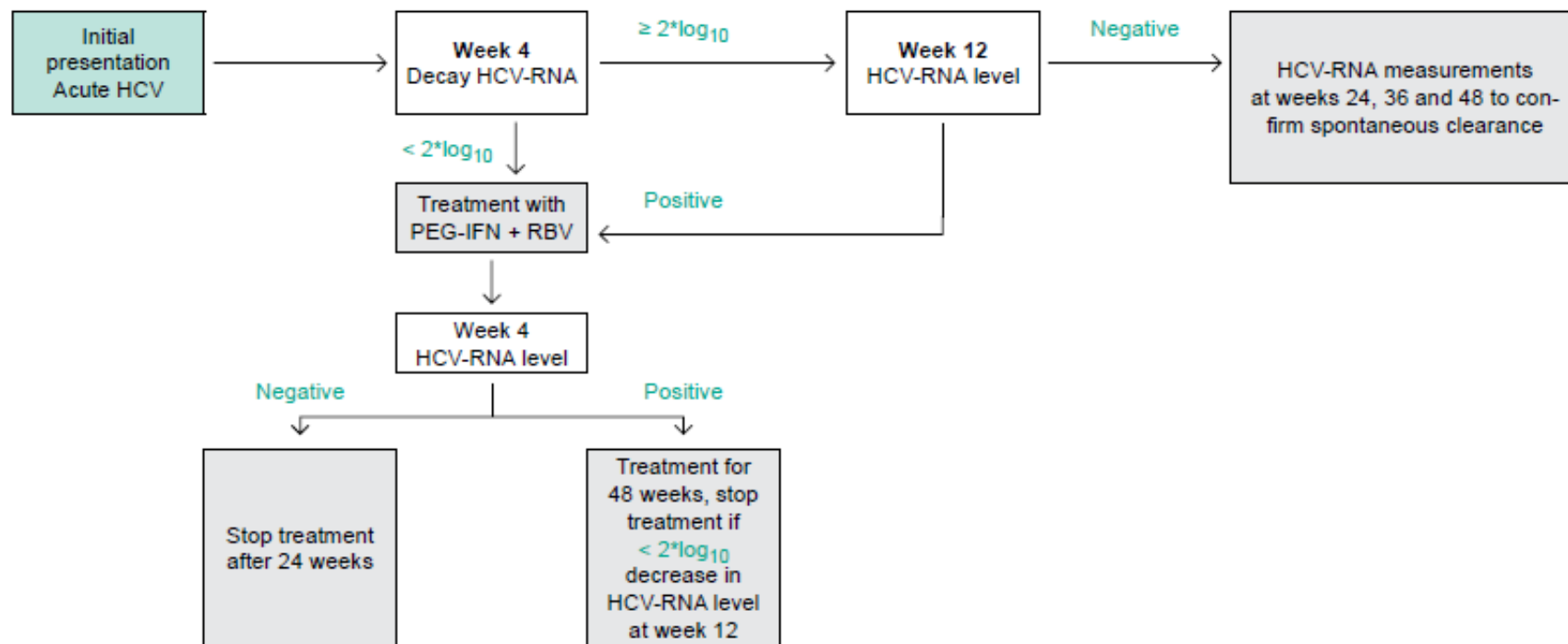


SVR12 rates



- Overall SVR12 currently 90% (454/503)

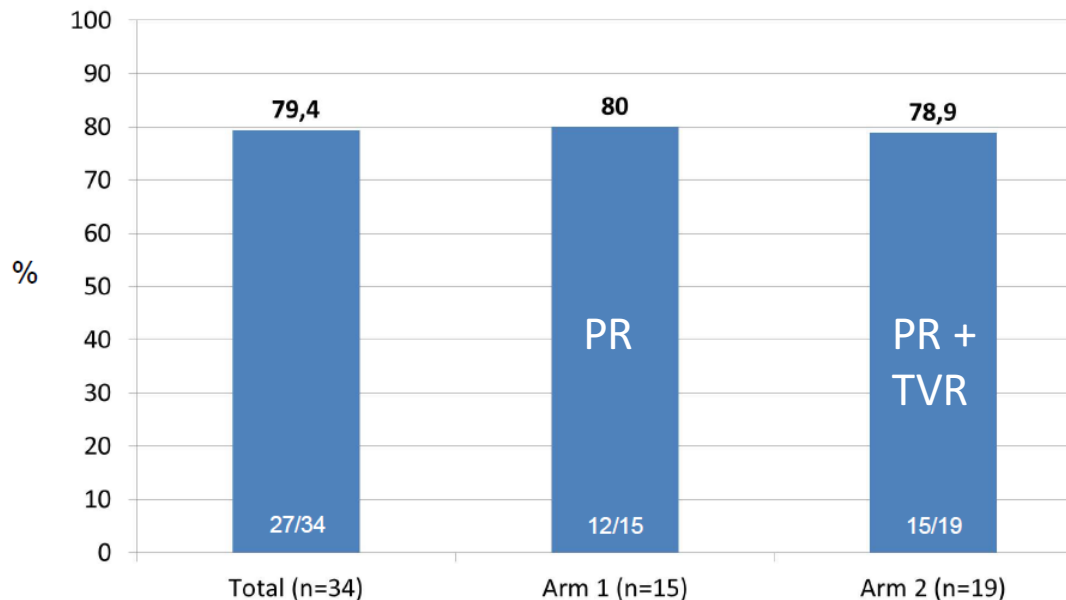
Algorithm for Management of Acute HCV in Persons with HCV/HIV Co-infection



Telaprevir Containing Triple Therapy in Acute HCV Coinfection: The CHAT Study

Christoph Boesecke^{1,2}, Gurmit K. Jagjit Singh³, Stefan H.-A. Scholten⁴, Thomas Lutz⁵, Axel Baumgarten⁶, Stephan M. Schneeweiss^{1,4}, Andreas Trein⁷, Michael Rausch⁸, Patrick Ingiliz⁶, Jürgen K. Rockstroh^{1,2}, Mark Nelson³ for the CHAT study group

Figure 2. SVR₁₂ rates overall and per study arm



- 1 viral breakthrough
- 2 non-responders
 - in one case HCV protease inhibitor associated mutations were selected under TVR (V36M,155K).

German GECCO Cohort: HCV-reinfections

- GECCO-Cohort (9 German centres)
- n=1483
- 24 re-infections
- Re-infection rate:
 - 11% (19/166) in MSM after median 45 weeks
 - 1% (5/454) in IVDU after median 40 weeks

Characteristics re-infected

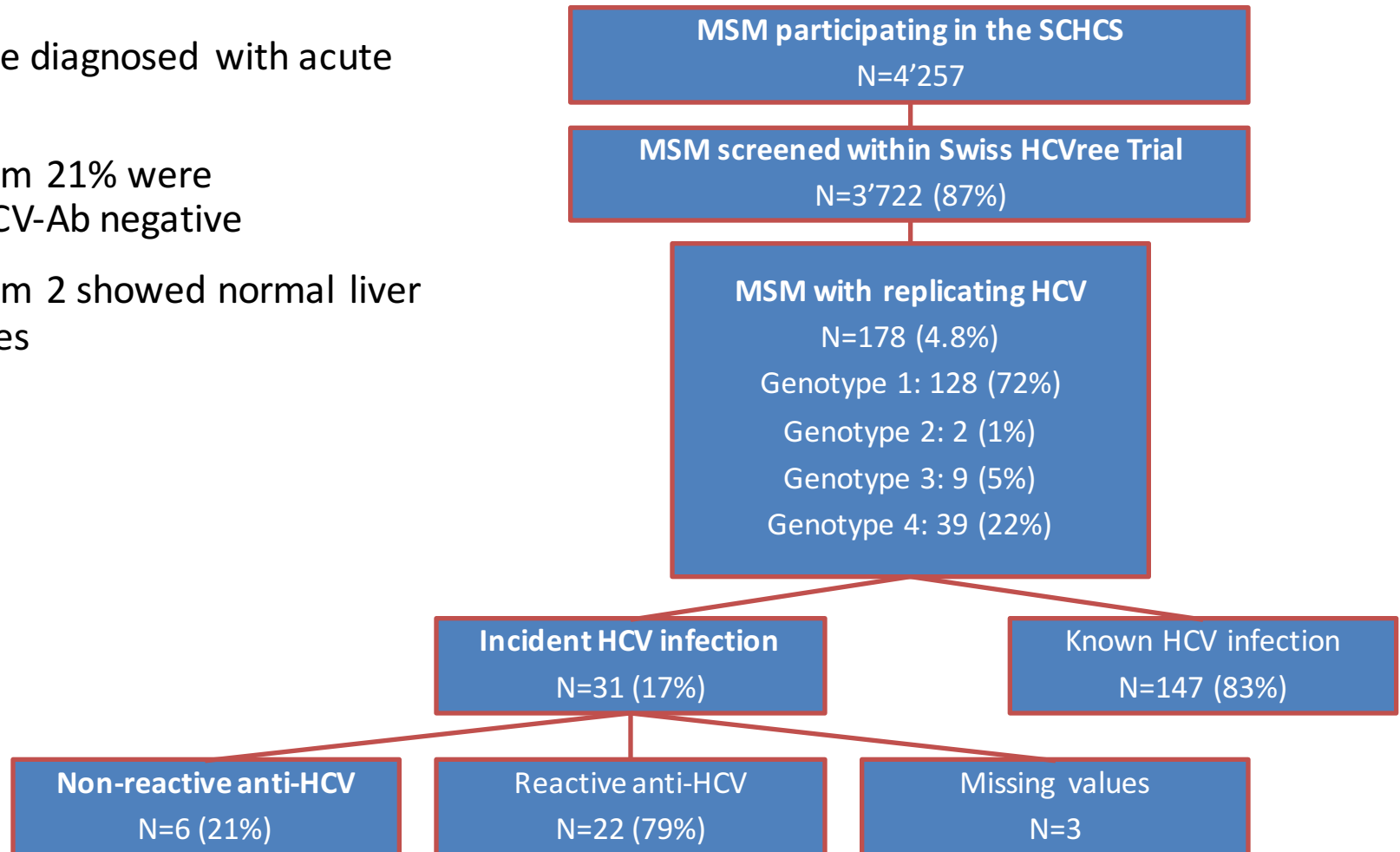
	Reinfection n = 24
Median Age [years (IQR)]	49 (42 – 54,5)
Male [n (%)]	24 (100)
Mode of HCV transmission	
• IVDU [n (%)]	5 (21)
• MSM [n (%)]	14 (58)
• MSM + IVDU [n (%)]	5 (21)
HIV coinfection [n (%)]	20 (83)
Median time to reinfection [weeks (IQR)]	41 (25 – 67)
Previous HCV treatment	
• SOF-PEG-RBV [n (%)]	7 (29)
• SOF/LDV [n (%)]	11 (46)
• PTV/r/OBV+/-DSV+/-RBV	2 (9)
• SOF/RBV	1 (5)
• SOF-DCV	2 (9)
• SIM-SOF	1 (5)

Swiss Cohort

Routine PCR-based HCV Screening

Study Flow Diagram

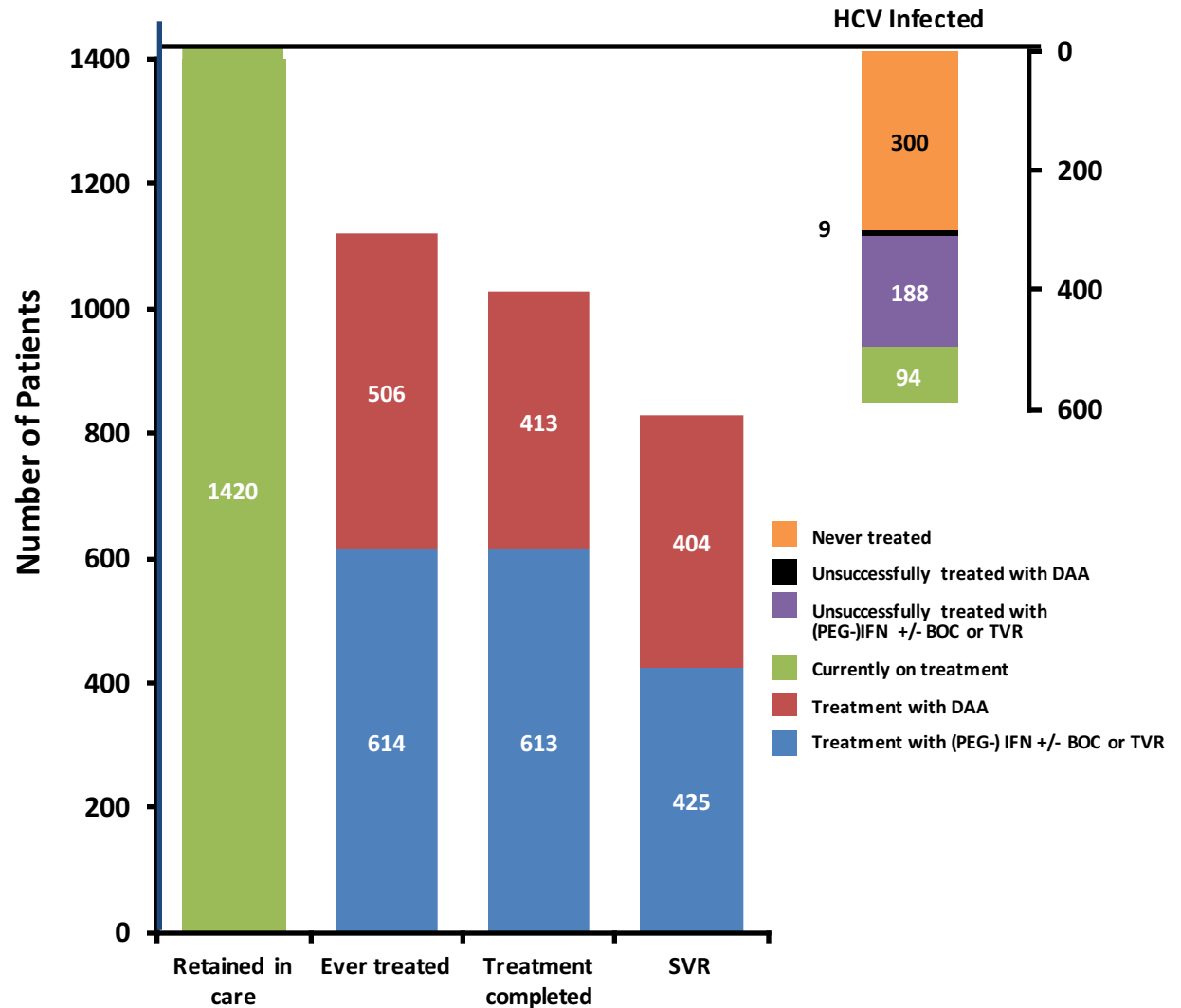
- 31 were diagnosed with acute HCV
- of whom 21% were anti-HCV-Ab negative
- of whom 2 showed normal liver enzymes



Dutch Athena Cohort

Rapid and early treatment uptake of DAAs

- Since 11/2015 unrestricted access to DAA
- Early treatment initiation in n=736
- 70% cure - Jan 2017



Dutch Acute HCV in HIV Study (DAHHS; 8 Centres)

Declining Acute HCV epidemic Due to DAA?

2014

A-HCV **n=93**

PYFU n=8290

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

1.1% per year

2016

A-HCV **n=49**

PYFU n=8961

5.5/1000PYFU (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

Jul-Dec 2016 4.0/1000



BUT: 41% Increase in Syphilis Cases in 2016 vs. 2015

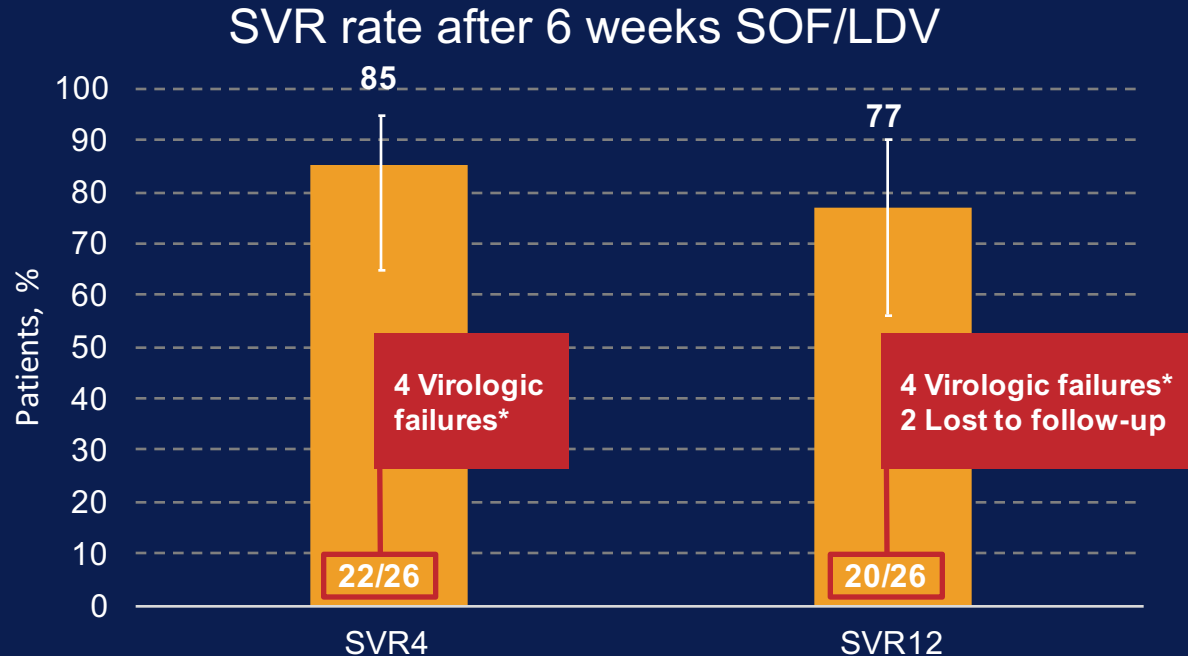
Treatment of acute HCV

12. In the absence of approved DAAs in the setting of acute HCV co-infection, treatment with PEG-IFN and RBV should be based on an individual decision weighing the known toxicities and longer treatment duration under dual therapy against a potentially strong wish from the co-infected person for early HCV cure, particularly in HIV-positive MSM with a higher risk of HCV transmission and in countries where DAAs will only be reimbursed in chronic HCV with $\geq F3$ fibrosis. After diagnosis of acute HCV, HCV-RNA should be measured 4 weeks later. Treatment can be discussed in persons without a decrease of $2 \cdot \log_{10}$ of HCV-RNA at 4 weeks compared with initial HCV-RNA and in persons with persistent serum HCV-RNA 12 weeks after diagnosis of acute HCV, see [Algorithm for Management of Acute HCV in Persons with HCV/HIV Co-infection](#). Early discontinuation of dual therapy is justified in persons experiencing significant side effects of PEG-IFN and/or RBV. Enrollment of persons with acute HCV co-infection in ongoing trials using IFN-free DAA combination therapy is strongly encouraged. In countries with access to DAAs and potentially individual cost reimbursement for DAAs in the setting of acute HCV, sofosbuvir/ledipasvir for 6-8 weeks has been proven to be successful. Treatment should be prolonged to 8-12 weeks in persons with high baseline HCV-RNA ($\geq 6 \log_{10}$ IU/mL).



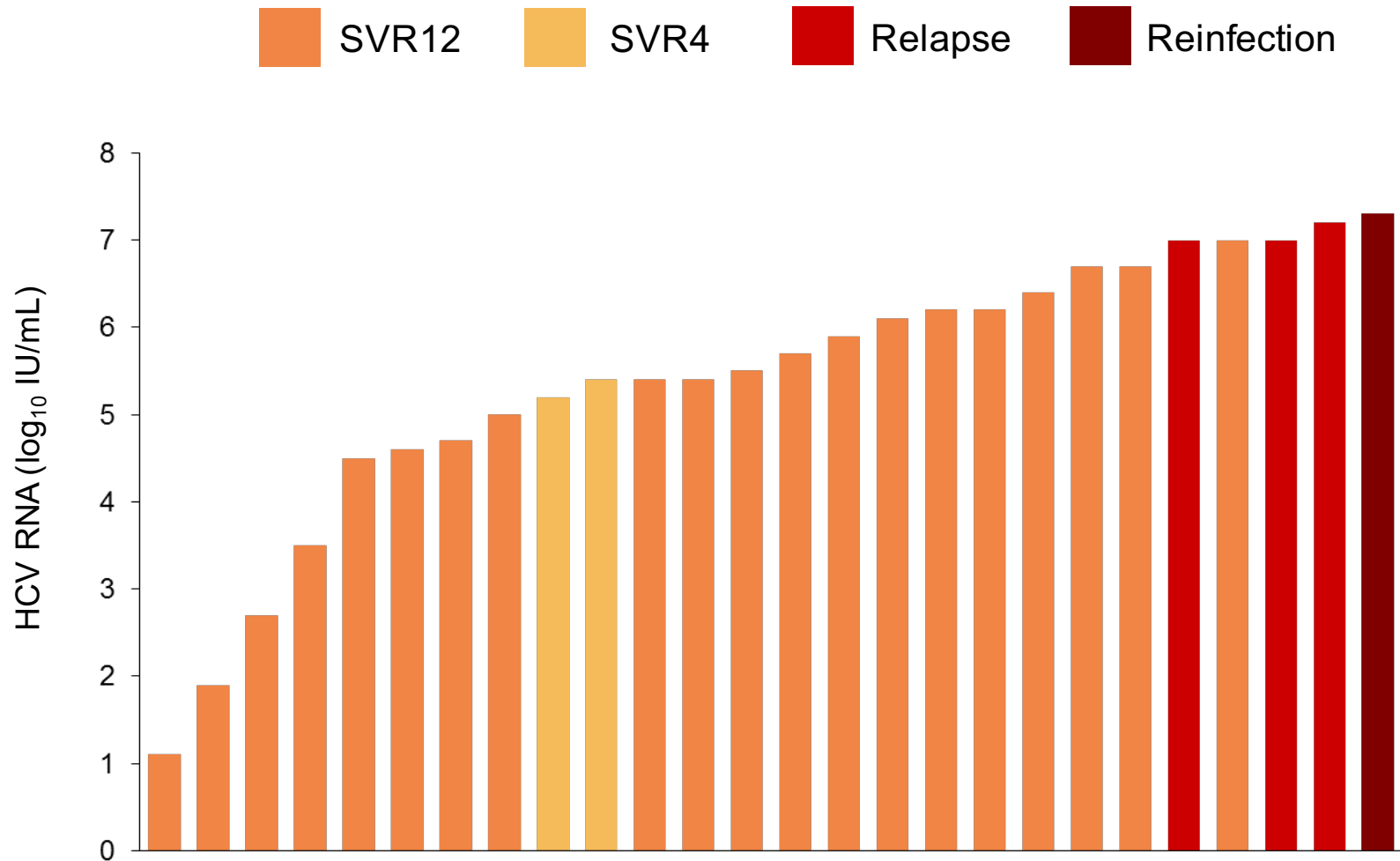
DAAs in acute HCV

- 26 HIV-infected patients with acute HCV GT 1 or 4
- HCV Ab/PCR negative in previous 6 months



4x virologic failure: 1x re-infection (GT1a ->4d), 3x relapse
→ high baseline HCV RNA, late treatment initiation

Baseline HCV RNA and SVR

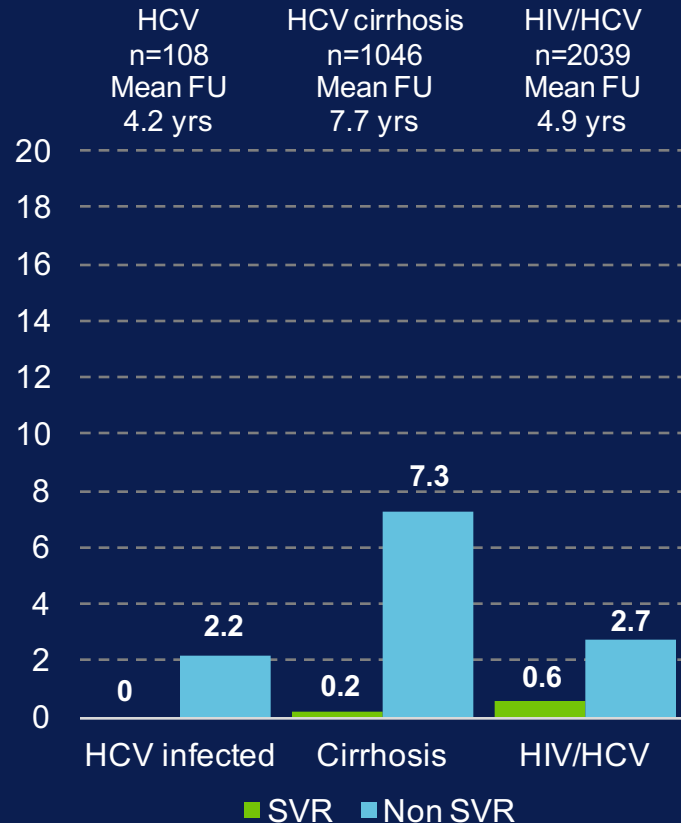


- SVR 100% in AHC mono-infection (n=20)

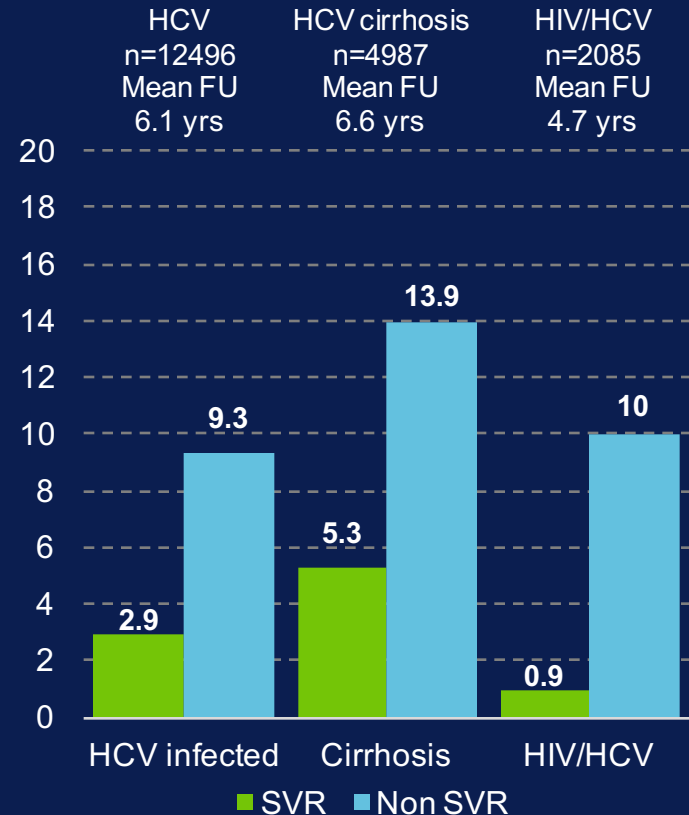
What happens after HCV cure?

Meta-analysis of 32 studies (33.360 patients)

Risk of liver transplantation after 5 years



HCC risk after 5 years



Beyond Hepatitis B & C

More than 20 cases of **acute hepatitis A virus infection** have been reported in Berlin, Germany. First cases were reported in Nov 2016.

Most infections have been **reported in MSM** in the age group 20 to 46.



Conclusions

- Switching from TDF to TAF appears to be safe and effective
- No evidence for an increased incidence of HCC with DAA use
- Patients with HIV/HCV coinfection and lower CD4-counts and cirrhosis show less favorable SVR rates
- Consider HCV-PCR for acute HCV diagnosis as HCV-Ab may still be negative
- Increased uptake of DAA therapy in acute and chronic HCV may help to decrease new HCV infections
- Pay attention to HAV/HBV vaccination

back-up

Diagnostic Procedures for HCV in Persons with HCV/HIV Co-infection

Diagnosis of HCV
HCV-Ab (turn positive 1-6 months after infection as late seroconversions have been described, may rarely be lost due to immunosuppression)
HCV-RNA levels ⁽ⁱ⁾ (in particular important for the prediction of response to IFN treatment)
Status of liver damage
Staging of fibrosis (e.g. FibroScan, liver biopsy, serum fibrosis markers ⁽ⁱⁱ⁾)
Hepatic synthetic function (e.g. coagulation, albumin, cholinesterase)
Ultrasound every 6 months if cirrhosis (gastroscopy upon diagnosis of cirrhosis and every 2-3 years thereafter if negative for oesophageal varices), see page 51
Before HCV treatment
HCV genotype (GT) ⁽ⁱⁱⁱ⁾ , HCV-RNA, renal and liver function tests
Autoantibodies (ANA, LKM1) ^(iv)
TSH, thyroid autoantibodies (risk of hyperthyroidism under IFN-based therapy)
Monitoring of HCV treatment
Differential blood count, creatinine, liver enzymes and, in persons with advanced fibrosis, bilirubin, albumin and INR every 2-4 weeks. In persons treated with IFN-free regimens HCV-RNA at 2-4 weeks and whenever needed in order to assess compliance and or breakthrough in persons experienced to oral DAAs.
HCV-RNA at week 4 (to evaluate rapid virological response (RVR) under IFN-based HCV regimens) and under all treatments at end-of-treatment and at week 12 and 24 after treatment cessation (to assess SVR). In persons receiving all oral DAA therapy no association between viral load at any given time-point under therapy and SVR has yet been found.
CD4 count and HIV-VL every 12 weeks
TSH and non-organ specific autoantibodies every 12 weeks under IFN-based therapy

- i Low HCV-RNA defined as < 400,000-600,000 IU/mL when using PEG-IFN+RBV. There is no standard conversion formula for converting the amount of HCV-RNA reported in copies/mL to the amount reported in IU/mL. The conversion factor ranges from about one to five HCV-RNA copies per IU/mL.
- ii Serum fibrosis markers include APRI, FIB-4, Hyaluronic acid, Fibrometer, Fibrotest, Forns, Hepascore and other indices; recently more complex tests such as Fibrometer, Fibrotest and Hepascore have shown to more accurately predict liver fibrosis than simple biochemical tests such as APRI, FIB-4 or Forns.
- iii Re-test for GT and sub-type should be performed in persons with tests carried out before second-generation tests were available (second-generation line-probe assay or real-time PCR assay) or in persons at risk of 'super-infection' for whom the GT/sub-type should be performed on most recent available specimen.
- iv Persons with positive anti LKM or ANA with homogeneous pattern should be evaluated for concurrent autoimmune hepatitis especially in the presence of ALT elevation during IFN-based treatment. Other concurrent causes of liver disease should be identified by blood tests and liver biopsy if needed.

