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BHIVA ‘Best of CROI’ Feedback Meetings

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HIV/hepatitis co-infection

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Royal Free London NHS Foundation Trust

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HIV/Hepatitis and Liver Disease

CROI 2016

BOSTON, MASSACHUSETTS

February 22-25, 2016

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Overview

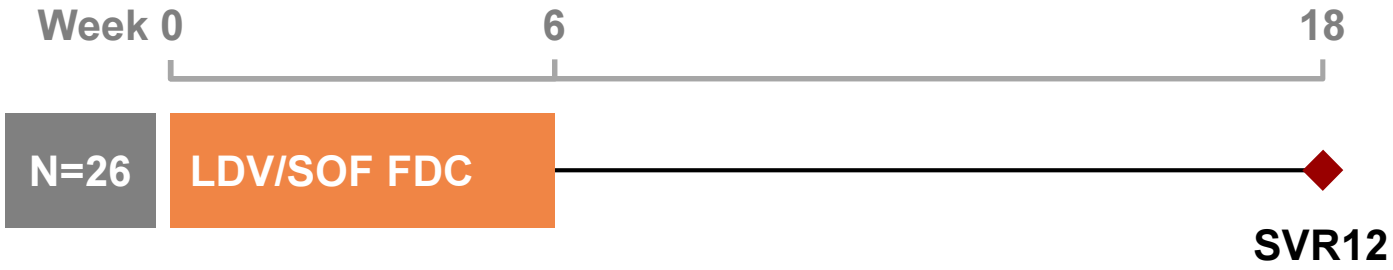
- HIV/HCV co-infection
  - Short duration DAA-based therapy for acute HCV in HIV+
  - NS5a RAVs, response to treatment and re-treatments
  - ‘Real-World’ data with DAAs
  - Next generation therapy
- HIV/HBV co-infection
  - Incidence of HBV in Uganda and ‘protective’ effect of TDF
- Non-viral liver disease
  - Statins and liver fat
  - Cenciviroc and liver fibrosis

Recent data for shortened duration therapy in acute/early HCV in HIV+

Study	Genotype	Number	Regimen	Duration	SVR12 (%)
DAHHS[1]	1a	57	BOC + PegIFN/RBV	12 weeks	86
NYC[2]	1	19	TVR + PegIFN/RBV	12 weeks	84
CHAT[3]	1	9	TVR + PegIFN/RBV	12 weeks	56
SWIFT-C[4]	1/4	17	SOF/RBV	12 weeks	59
DARE-C II[5]	1/3	14	SOF/RBV	6 weeks	21
NYC II[6]	1	12	SOF/RBV	12 weeks	92
SLAM-C Arm 1[7]	1	15	SOF/LDV	6 weeks	100
SLAM-C Arm 2[7]	1	15	SOF/SMV	8 weeks	100

1. Hullegie, J Hepatol 2015; doi 10.1016/jhep.2015.12.004. [Epub ahead of print]. 2. Fierer, Clin Infect Dis; 2014; 58: 873-9. 3. Boesecke, unpublished (personal communication). 4. Naggi, A1094, AASLD 2015, San Francisco CA. 5. Martinello, A1083, AASLD 2015, San Francisco CA. 6. Fierer, A1090, AASLD 2015, San Francisco CA. 7. Basu, A1074, AASLD 2015, San Francisco, CA

Ledipasvir/Sofosbuvir for 6 Weeks in HIV-infected Patients with Acute HCV Infection



- Patients with chronic HIV and acute HCV infection
  - HCV GT 1 or 4
  - ART consistent with LDV/SOF co-administration with HIV <200 copies/mL or not receiving ART with no plans to start
- Acute HCV infection with detectable HCV RNA (Roche COBAS® AmpliPrep/COBAS® TaqMan® version 2.0, LLOQ=15 IU/mL) for <24 weeks, defined by
  - HCV RNA-positive and negative anti-HCV antibody/HCV RNA test within last 6 months or
  - Elevated ALT/AST >2.5 x ULN in past 6 months with normal LFTs in past year, and other causes excluded
- 5 sites in Germany and UK

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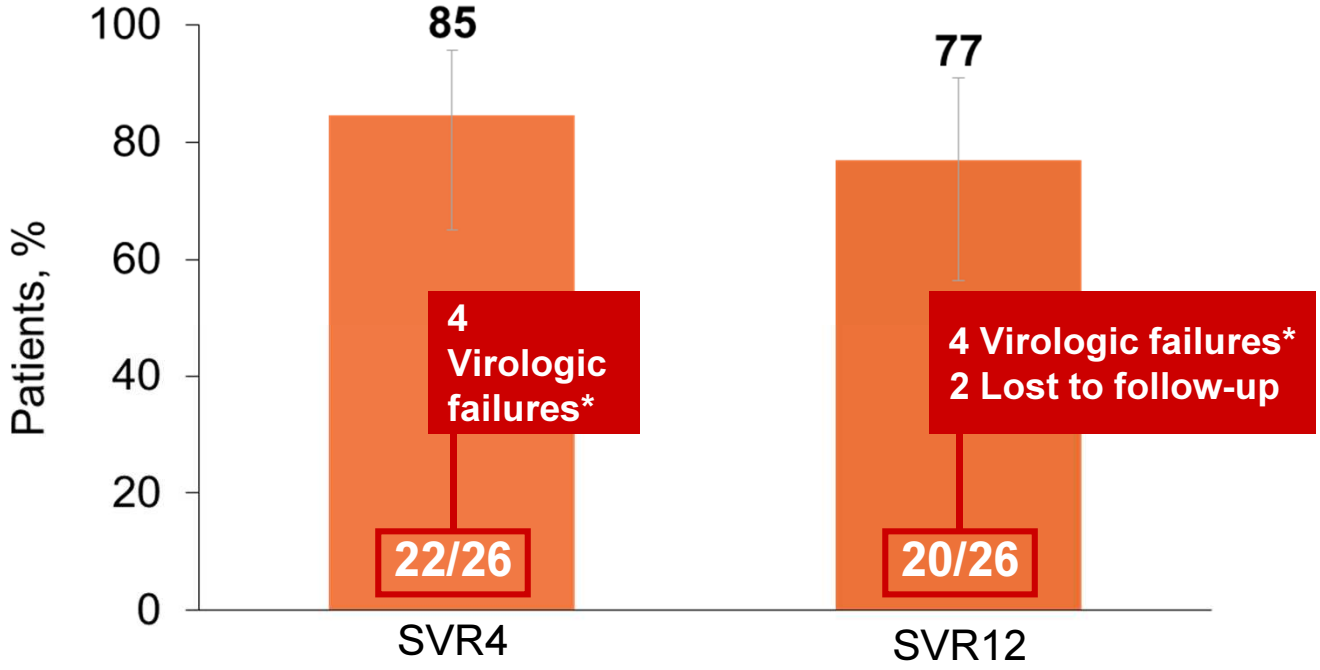
Rockstroh, J et al. CROI 2016; Boston #154LB

SVR4 and SVR12



GT (LiPA)	Baseline HCV RNA, log_{10} IU/mL	IL28B	BMI, kg/m^2	Duration of Infection, weeks
4	7.1	CT	24	24.5
1a	7.0	CT	22	N/A
1a	7.2	CT	21	22.5

*3 patients relapsed, 1 was reinfected (GT 1a at baseline, 4d in post-treatment).
Error bars represent 95% confidence intervals.

Rockstroh, J et al. CROI 2016; Boston #154LB

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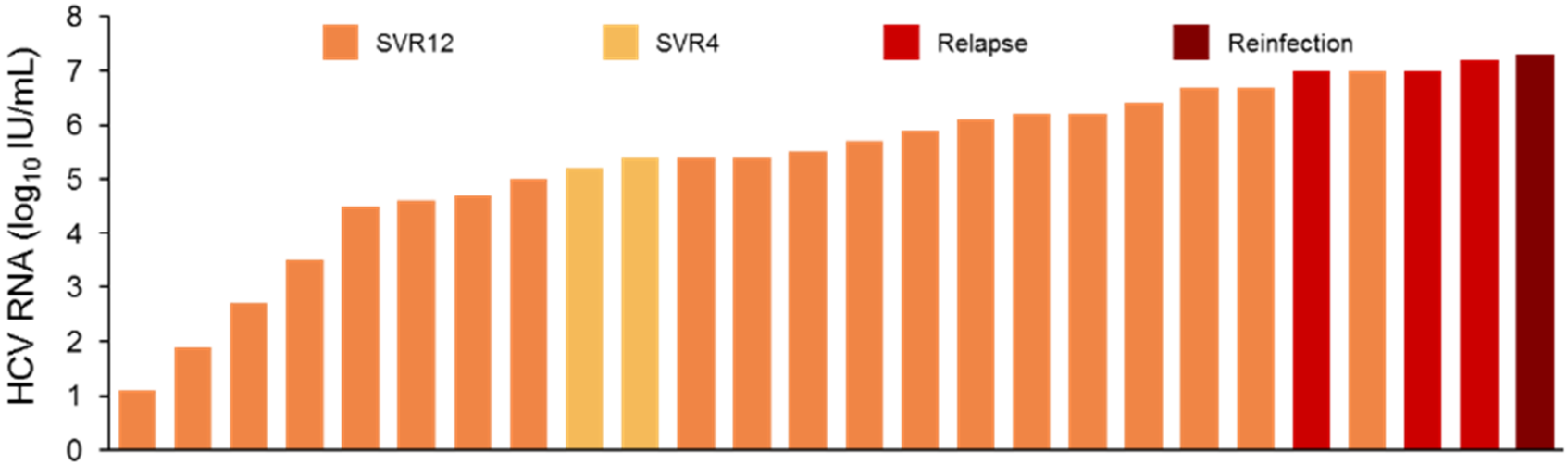
Results: Baseline HCV RNA and Treatment Outcome (SVR)



Conclusions

- 77% SVR12 rate with 6 weeks of LDV/SOF in HIV+ patients with acute HCV infection
  - No relapse among patients with a baseline HCV RNA <9 million IU/mL
  - Reinfection in 1/26 patients followed through post-treatment Week 12
- Treatment with LDV/SOF for 6 weeks was well tolerated with similar safety profile for boosted and un-boosted TDF-based regimens
- Acutely HCV-infected patients with a higher viral load should be considered for longer duration of therapy

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Rockstroh, J et al. CROI 2016; Boston #154LB

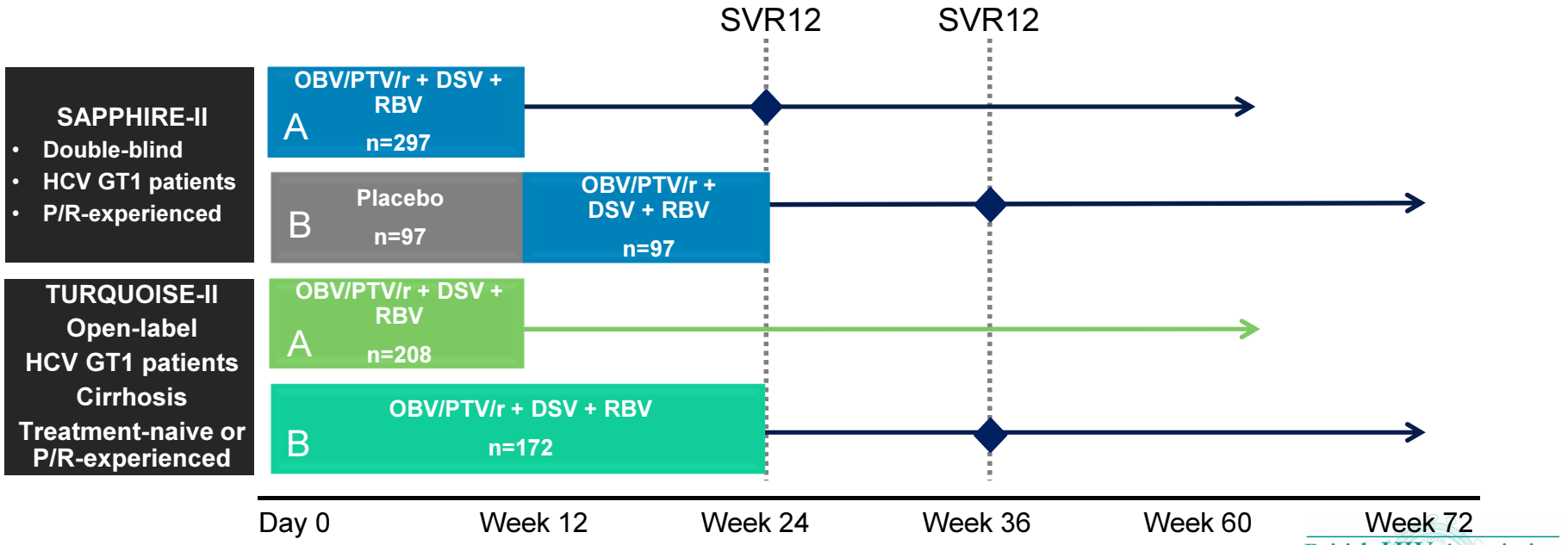
Acute HCV – take home messages

- Shorter duration therapy with TWO DAAs may be possible in the context of early HCV
- However, HCV viral load is key determinant of success

- Upcoming trials with other DAAs and 8 weeks of therapy will address these issues.

DAA Resistance: GT1a Patient Populations Analyzed in Sapphire-II and Turqouise-II

- Included: Patients treated with label-recommended regimens for GT1a
- 214 GT1a patients from arms A and B of SAPPHIRE-II (no cirrhosis)
- 118 GT1a patients from arm B of TURQUOISE-II (compensated cirrhosis)
- Excluded: GT1a patients (n=9) who did not achieve SVR for reasons other than virologic failure (breakthrough or relapse)



Sulkowski M, et al. 23rd CROI; Boston, MA; February 22-25, 2016. Abst. 539LB.

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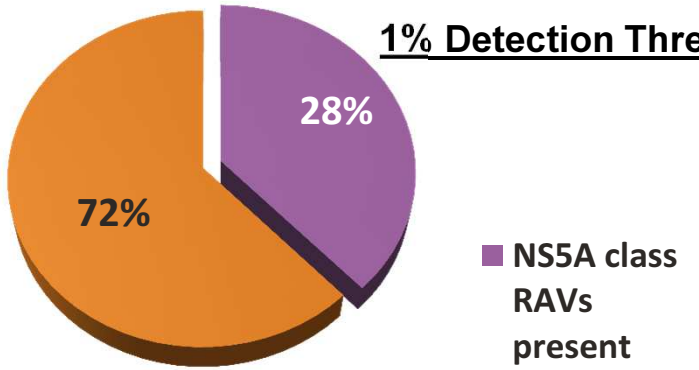
Prevalence of Baseline GT1a NS5A RAVs: Impact of RAV Definition and Sensitivity of Detection

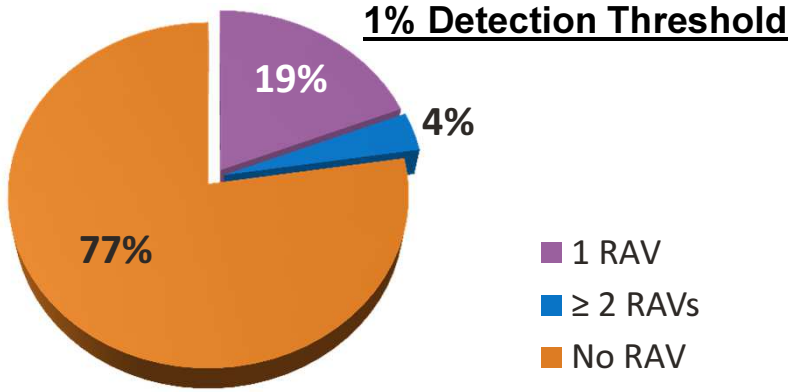
NS5A Inhibitor Class RAVs detected in this study at amino acid positions:

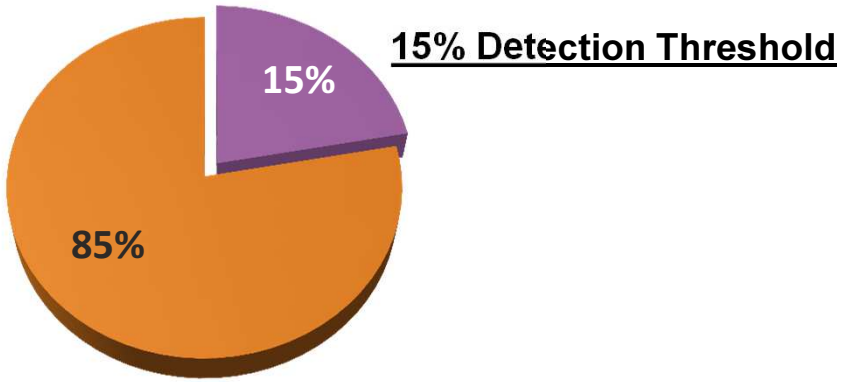
M28(all), Q30(all), L31(all), P32L, H58D/R, and Y93(all)

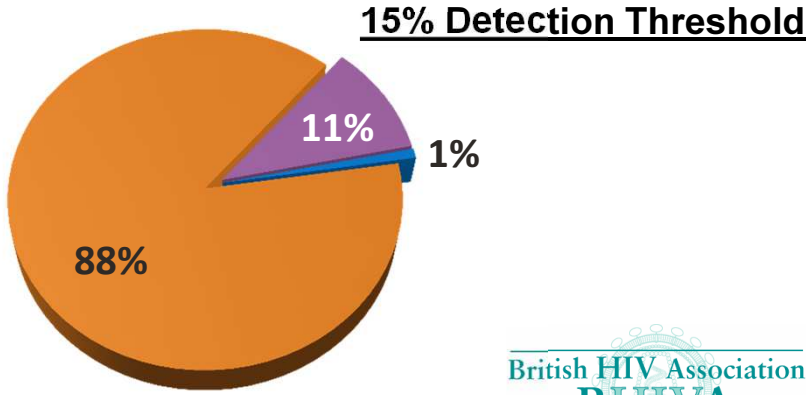
Ombitasvir-specific RAVs detected in this study:

M28T/V, Q30E/R, H58D, Y93C/F/H/L/N









Sulkowski M, et al. 23rd CROI; Boston, MA; February 22-25, 2016. Abst. 539LB.

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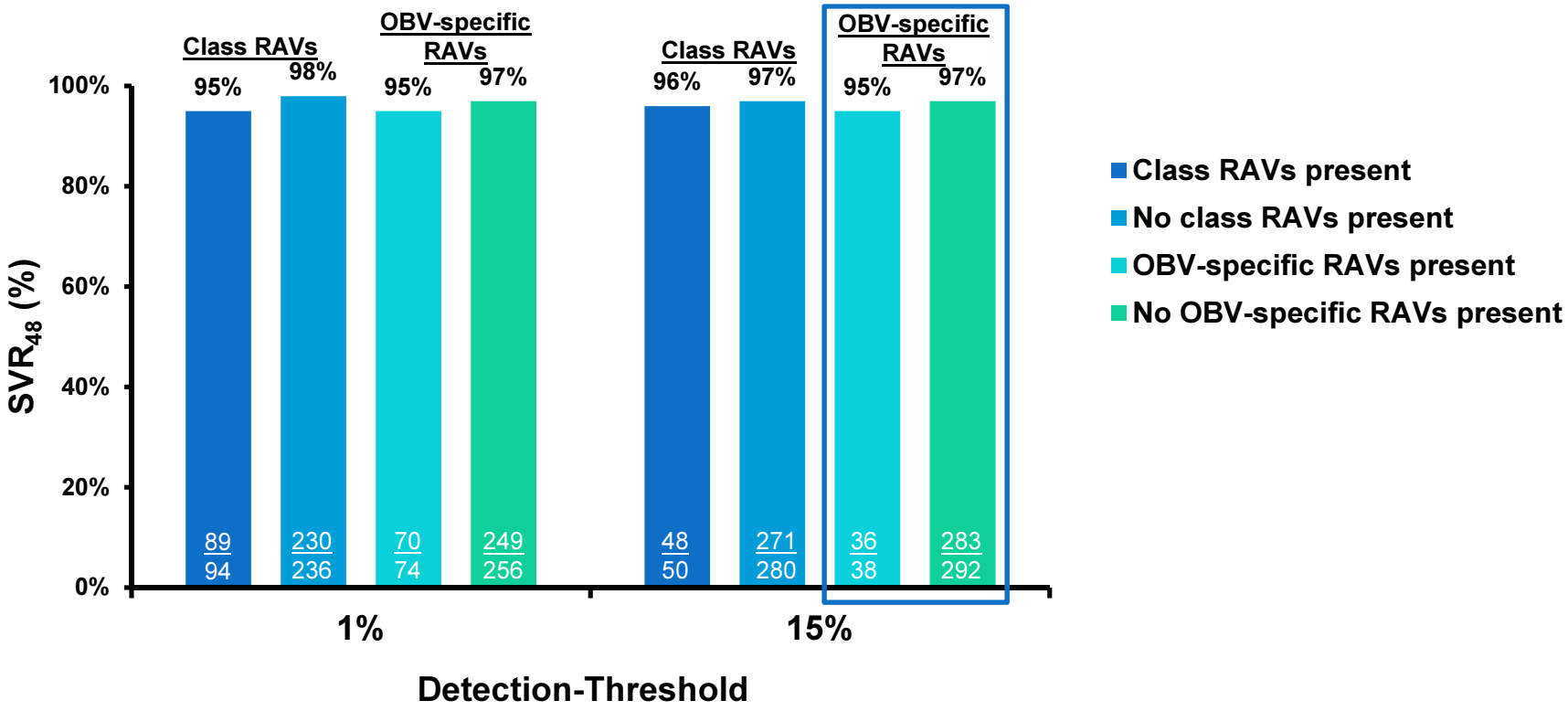
Impact of Baseline GT1a NS5A Class RAVs and Ombitasvir-specific RAVs on SVR Rate



- Similar SVR rates were observed irrespective of the presence or absence of baseline variants

Sulkowski M, et al. 23rd CROI; Boston, MA; February 22-25, 2016. Abst. 539LB.

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Re-treatment after failure to LDV/SOF

- 9 patients without SVR in ION-4 after 12 weeks of LDV/SOF

GT	NS5A RAVs Before Primary Study (%)	NS5A RAVs at Virologic Relapse After Primary Study (%)	SRV12
1a	None	None	Yes
1a	None	None	Yes
1a	L31M (>99), H58D (92)	L31M (>99), H58D (92)	Yes
1a	Y93F (1), Y93N (10)	Y93N (<99)	Yes
1a	L31M (>99), Y93N (<25)	L31M (>99), Y93N (>99)	Yes
1a	None	Y93N (>99)	Yes
1b	Y93H (>99)	L31I (11), Y93H (>99)	Yes
1b	None	L31V (>99)	Yes
1a	None	L31M (>99)	No

- 1 relapse 4 weeks after EOT: GT1a, no cirrhosis

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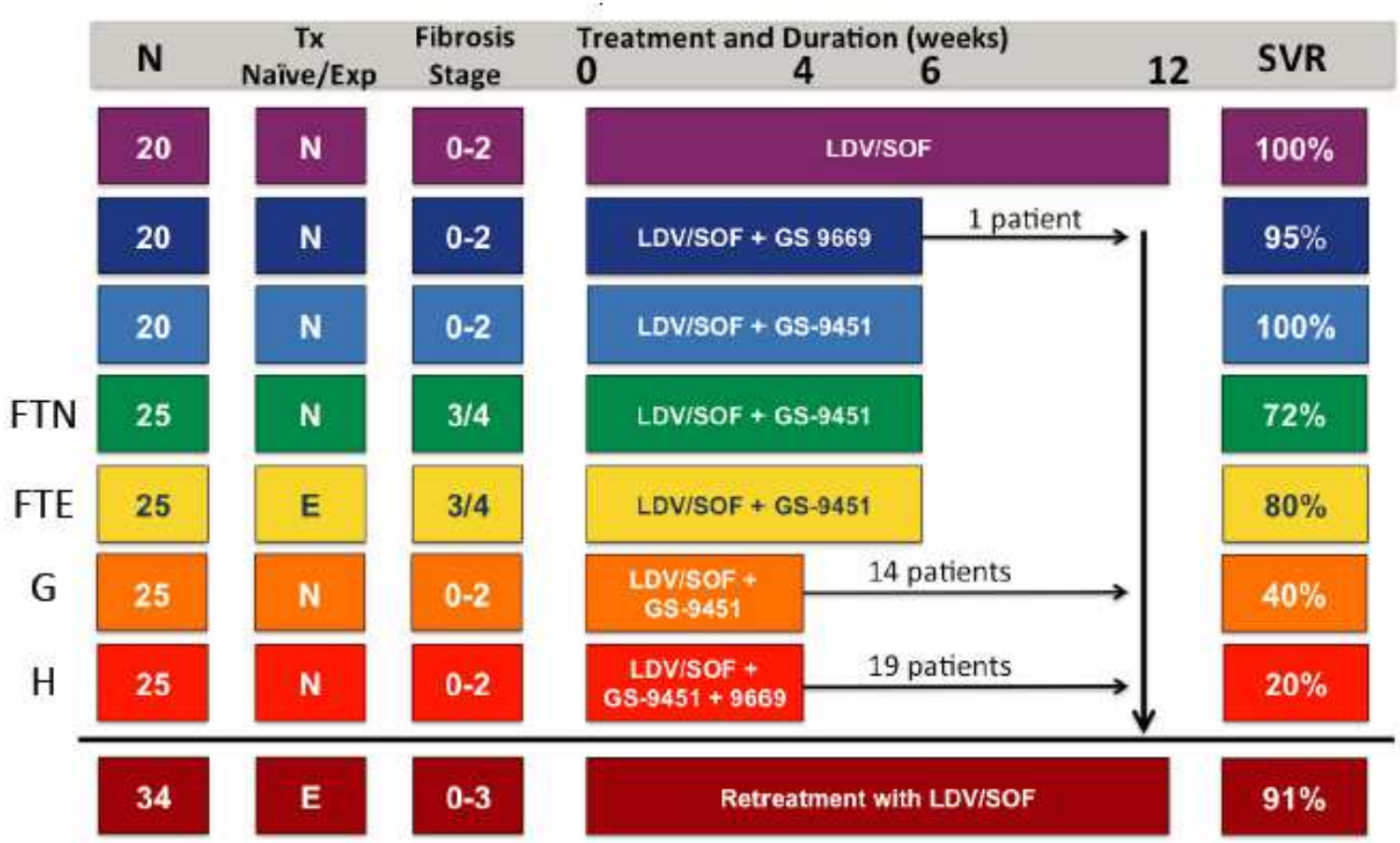
Cooper C, et al. 23rd CROI; Boston, MA; February 22-25, 2016. Abst. 573.

Resistance Associated Variants: Data From the NIAID SYNERGY Trial

NIAID SYNERGY is an 8 arm clinical trial that treated over 200 hepatitis C patients with varying ledipasvir (LDV) and sofosbuvir(SOF) based DAA regimens



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Wilson, E et al. CROI 2016; Boston #580

NAIAD Synergy: Baseline RAV Prevalence and Outcome, By Study Arm

RAV interpretation by genotype

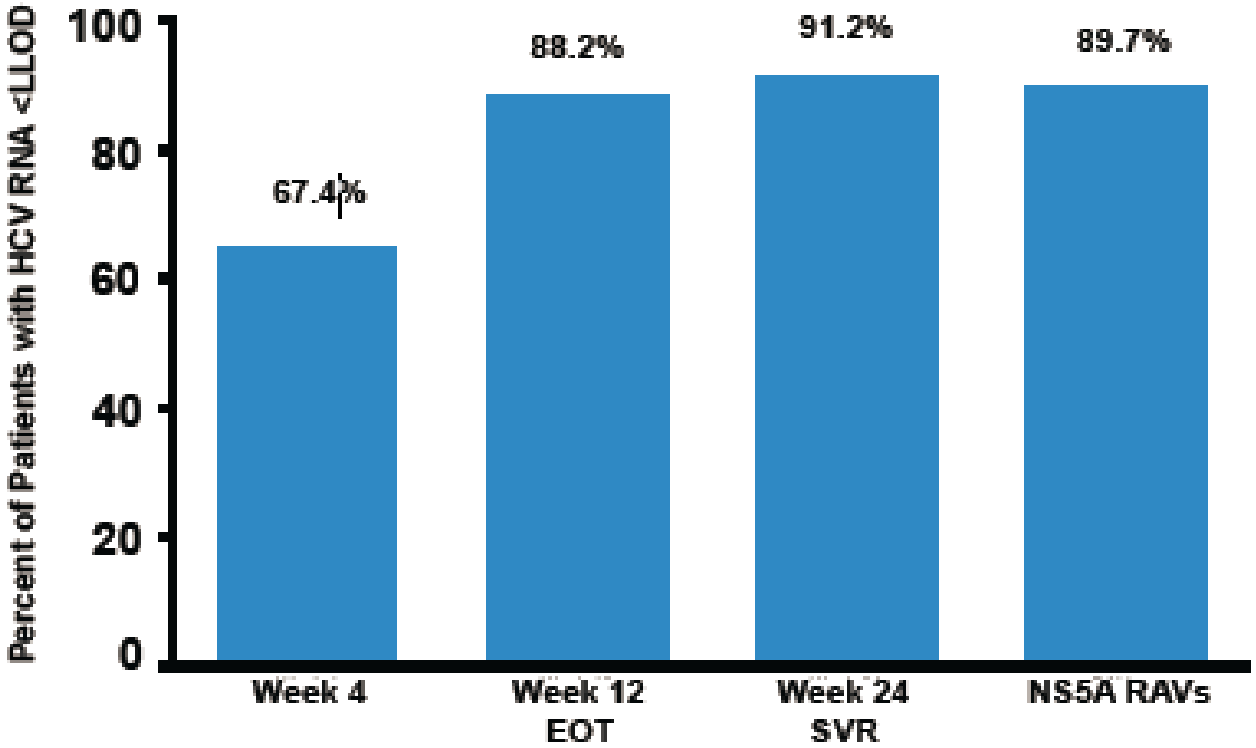
	SVR		NS3		NS5A		NS5B	
FTN	72%	Prevalence	8/25	32%	3/25	12%	-	
		SVR	5/8	63%	2/3	67%		
FTE	80%	Prevalence	11/25	44%	5/25	20%	-	
		SVR	10/11	91%	3/5	60%		
G	40%	Prevalence	8/25	33%	2/25	8%	-	
		SVR	4/8	50%	0/2	0%		
H	20%	Prevalence	5/24	21%	6/24	25%	1/24	(4%)
		SVR	0/5	0%	0/6	0%	1/1	(100%)

Of 160 patients treated initially, 99 patients had baseline RAV testing available

Wilson, E et al. CROI 2016; Boston #580

NIAID SYNERGY Trial

Retreatment of Relapsed Patients



- HCV NS5A RAVs do not predict relapse when using sofosbuvir-based treatment for at least 6 weeks or during re-treatment with standard 12 week regimens of LDV/SOF
- NS5A RAVs do appear to impact treatment response when treating with ultra-short, 4 week duration therapies

Wilson, E et al. CROI 2016; Boston #580

HCV Resistance Associated Variants (RAVs) – Take Home Messages

- RAVs – especially NS5A RAVs are common variants at baseline
- NS5A RAVs emerge at treatment failure and because of relative fitness – persist
- In general
  - Baseline RAVs NO impact on response to 12 weeks+ therapy with 3 drugs (PrOD), 8-12 weeks of SOF-containing dual therapy and 6 weeks of SOF-containg triple therapy
  - However, baseline RAVS negative impact on 4 weeks of Sof-containing triple therapy
- Resistance testing at failure may be worth doing BUT most patients can be re-treated with ADDITION of RBV or LONGER duration of same therapy

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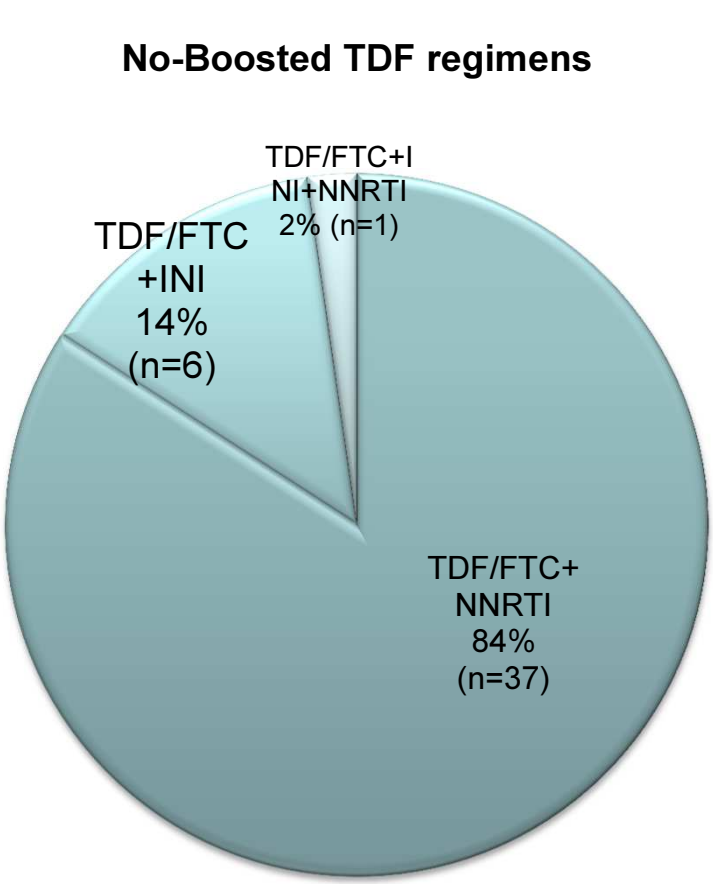
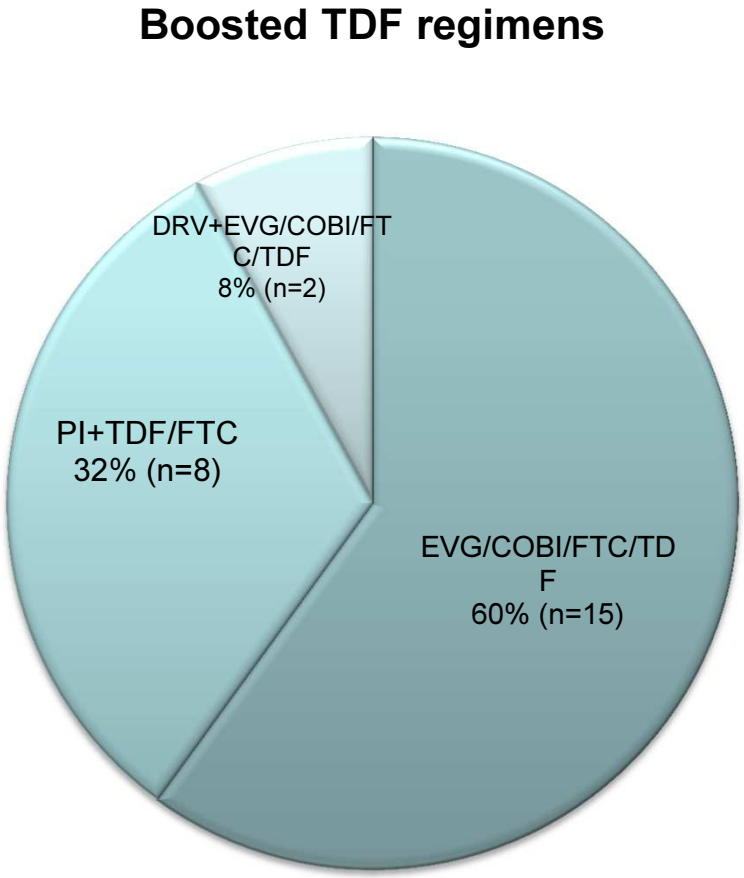
Real-life safety of 'boosted-TDF' in HIV/HCV patients on SOF/LDV





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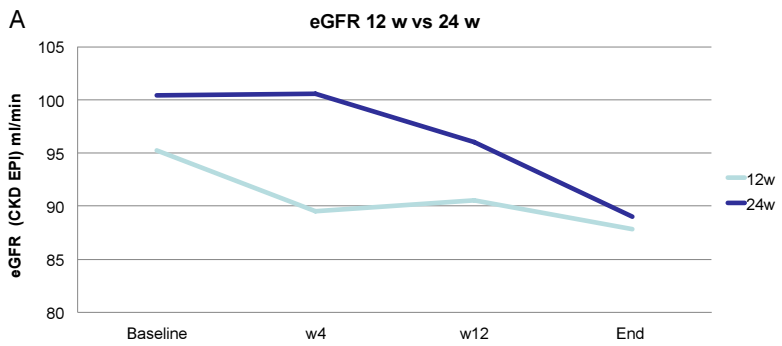
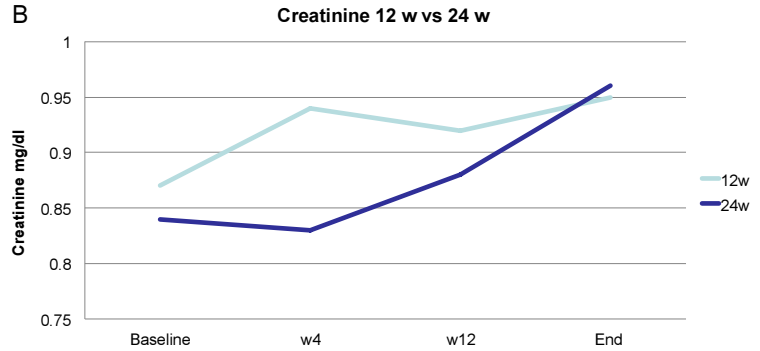
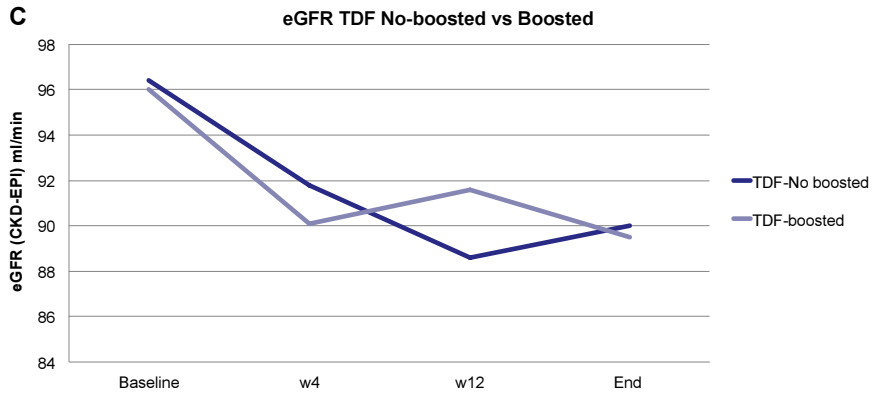
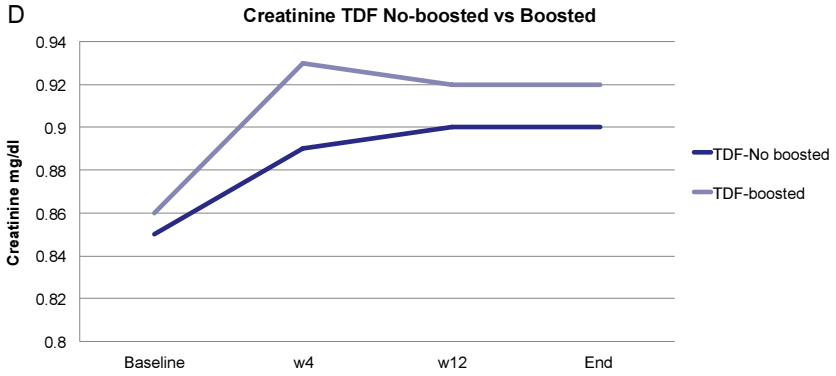
Vivancos-Gallego, E et al. CROI 2016; Boston #

Results









CKD-EPI eGFR (ml/min)	Baseline eGFR (ml/min) mean±SD	Baseline <70 ml/min n (%)	End-treatment eGFR (ml/min) mean±SD	End-treatment <70 ml/min n (%)
TDF-No boosted (n=44)	96±12	**1** (2%)	90±15	**1**+1 (4%)*
TDF-Boosted (n=25)	96±11	0 (0%)	88±17	3 (12%)**

* eGFR: 63ml/min; 69 ml/min **eGFR: 56 ml/min; 61 ml/min; 63 ml/min

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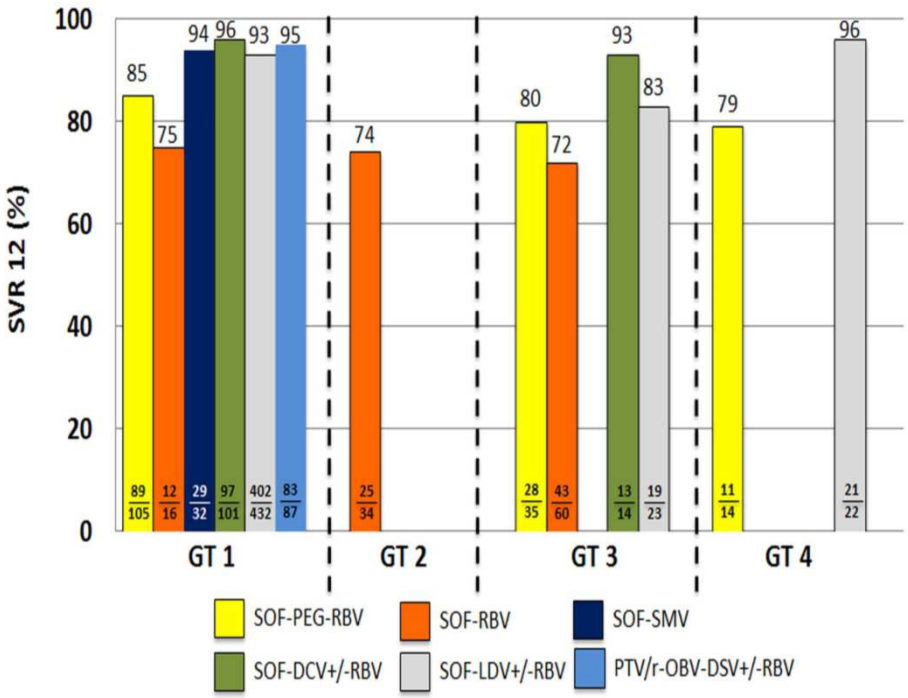
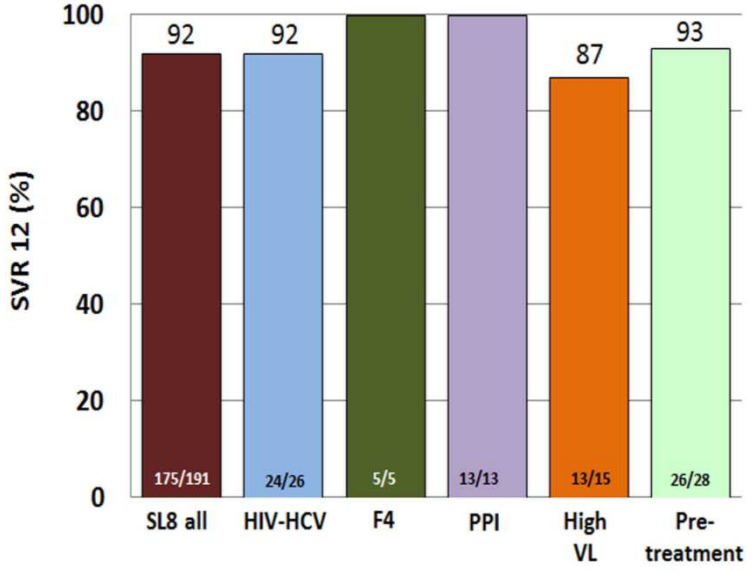
GECCO cohort

Direct acting agents against HCV: results from the German Hepatitis Cohort





Metavir F4 defined as APRI > 2 OR Fibroscan > 12.5kPa, high VL load defined as > 2mio IU/ml (Abbott PCR) or 6 mio IU/ml (Roche PCR), pretreatment was interferon-based (in one case with sofosbuvir); SVR, sustained virological response; APRI, AST-to-platelets ratio index; VL, viral load; PPI, Protonpump inhibitor use at baseline

- 1346 patients from 9 centres – 21% HIV/HCV co-infected, 29% F4/cirrhosis
- Real-life DAA-based treatment regimens are highly effective in HCV-mono- as well as HIV-HCV-coinfected patients
- Relapse occurred in only 4% of the patients. All DAA combinations were generally well tolerated
- In particular, SOF/LDV for 8 weeks seems highly effective in selected patients in this population.

Christensen S, E et al. CROI 2016; Boston #584

Real Life DAA Data from Egypt

- Almost 200 000 HCV patients already treated with DAAs in 2015 -> response rates similar to real life data from Europe/US
- Two main drivers: Purpose-built medical network and low drug costs:

Protocol	Applied for treatment	Started	ETR				SVR			
			Neg	Pos	Total	%	Neg	Pos	Total	%
Triple	41056	23754	15510	238	15748	98%	6846	364	7210	94%
SOF/RBV	24178	17474	9560	112	9672	98%	3370	1165	4535	74%
SOF/SIM	42821	11382	6176	96	6272	98%	1015	34	1049	97%
SOF/DAC	17930	1085								
SOF/DAC/RBV	15386	794								

El-Sayed M, et al. 23rd CROI; Boston, MA; February 22-25, 2016. Abst. 65.

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Real-life data – take home messages

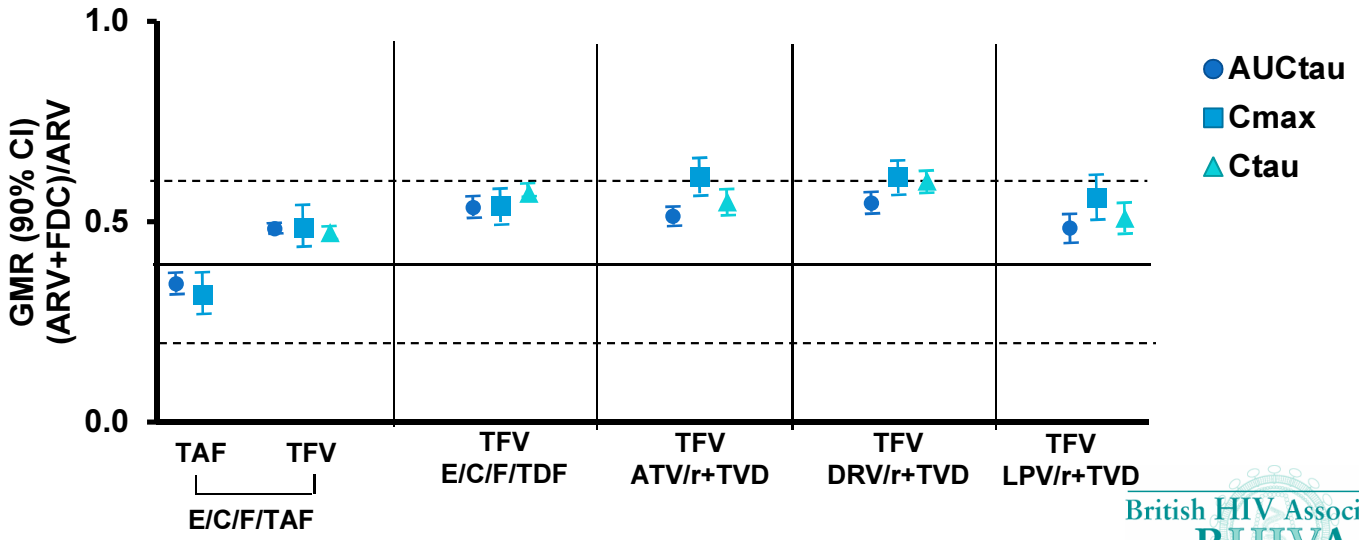
- No real renal issues with use of TDF + cobi/ritonavir-boosted-regimens and SOF/LDV
- DAA based therapy similar results in ‘real-world’ cohorts and phase 3 trials
- Shorter duration (8 weeks) of Sof/LDV may be possible in HCV/HIV co-infected patients
- Mass treatment strategies with similar results are possible
  - 200 000 patients treated already in Egypt
  - Compared to recent commissioning of NICE-approved DAA-based treatment for 10 000 non-cirrhotic patients 2016/7 – NHS England!

Interactions with Boosted ART/TAF and velpatasvir

- Phase 1 studies in 123 HIV-uninfected:

Cohort 1, n=24	SOF/VEL	+	EVG//COBI/FTC/TAF 150/150/200/10 mg
Cohort 2, n=24	SOF/VEL	+	EVG//COBI/FTC/TAF 150/150/200/300 mg
Cohort 3, n=24	SOF/VEL	+	ATV 300 mg + RTV 100 mg + FTC/TDF 200/300 mg
Cohort 4, n=30	SOF/VEL	+	DRV 800 mg + RTV 100 mg + FTC/TDF 200/300 mg
Cohort 5, n=24	SOF/VEL	+	LPV/RTV 800/200 mg + FTC/TDF 200/300 mg

- No significant influence of SOF/VEL on TAF



Mogalian E, et al. 23rd CROI; Boston, MA; February 22-25, 2016. Abst. 100.

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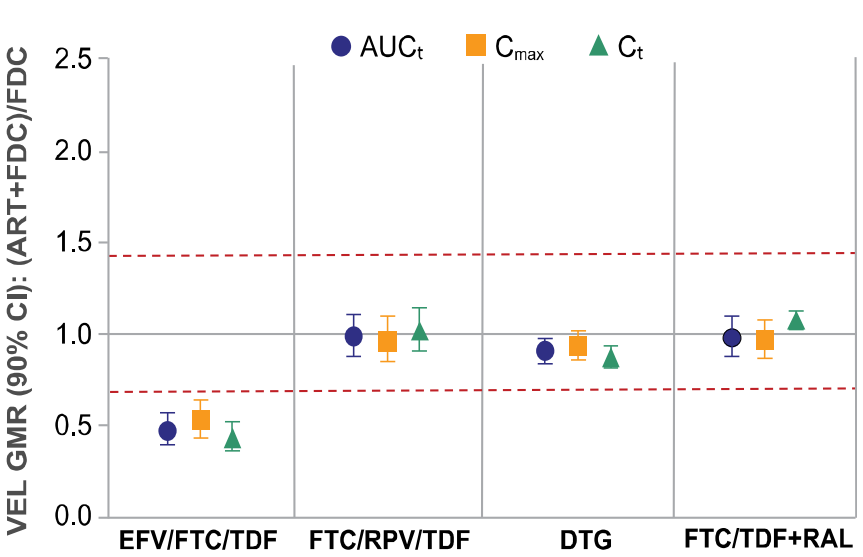
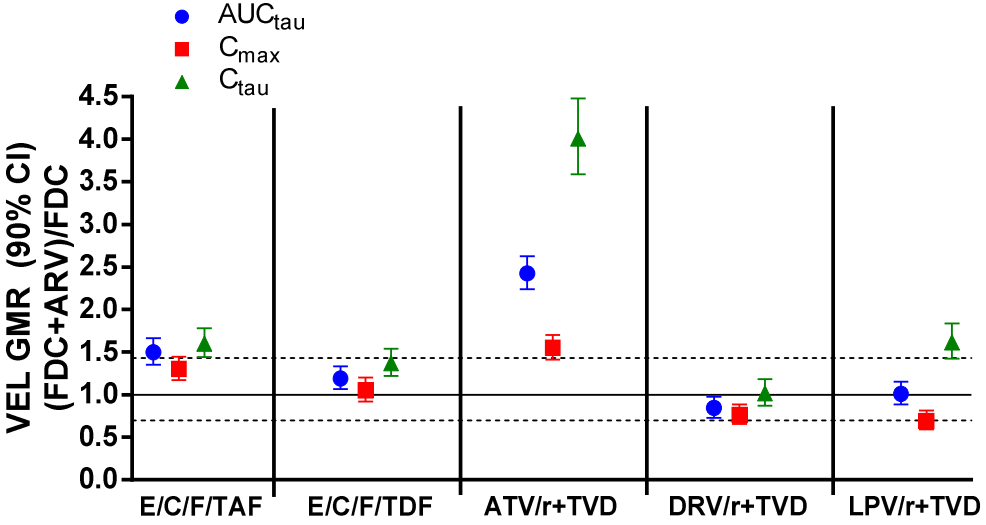
Effect of ARVS on VEL PK





- No significant impact of SOF/VEL on TAF or TFV derived from TAF
- Modest increase in TFV exposure (~20-40%) when administered as TDF (plus PI/r) in presence of SOF/VEL
  - Mechanism likely inhibition of efflux transport (e.g., P-gp)
- 70-100% increase in cobi levels with SOF/VEL, but because of the short 3h half-life of cobi this increase does not have any clinically significant potential for DDIs (actual AUC increase 20-30%)
- USE with EFV NOT RECOMMENDED (significant decrease in VEL PK)

*TVD, FTC/TDF
**Dotted lines* depict no-PK-alteration boundary.

Mogalian, AASLD, 2015, Presentation # 2265, Mogalian, CROI, 2016, Presentation # 100

ABT-493 and ABT-530 and RAL, RPV

Figure 3. Interaction between ABT-493 and ABT-530 with Rilpivirine (Central Value Ratios and 90% CIs)

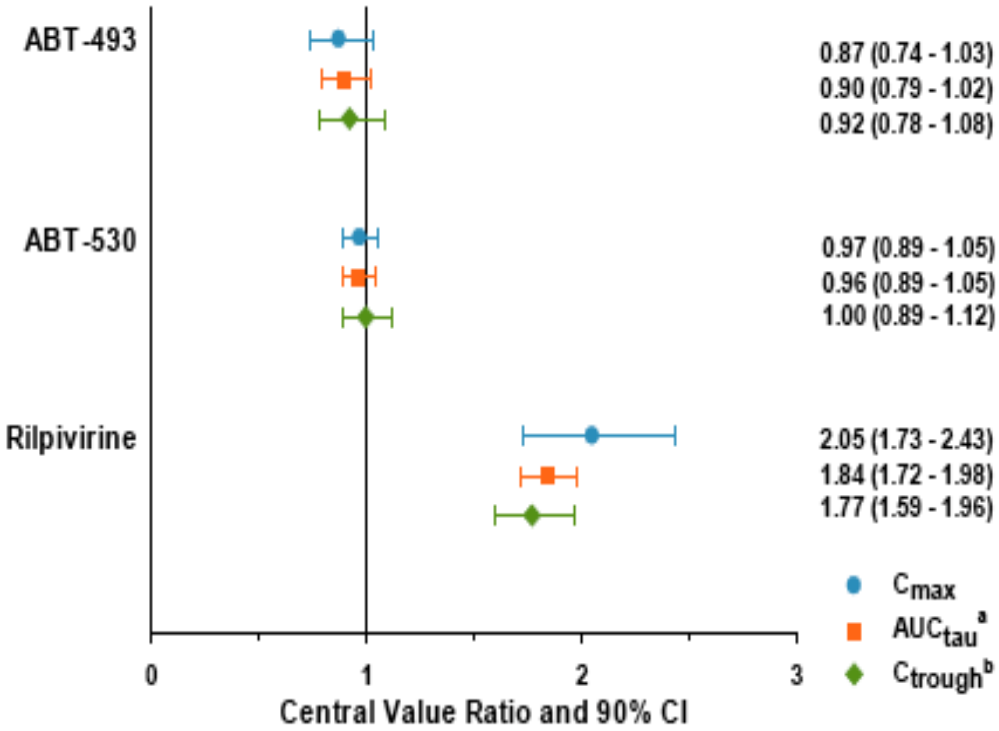
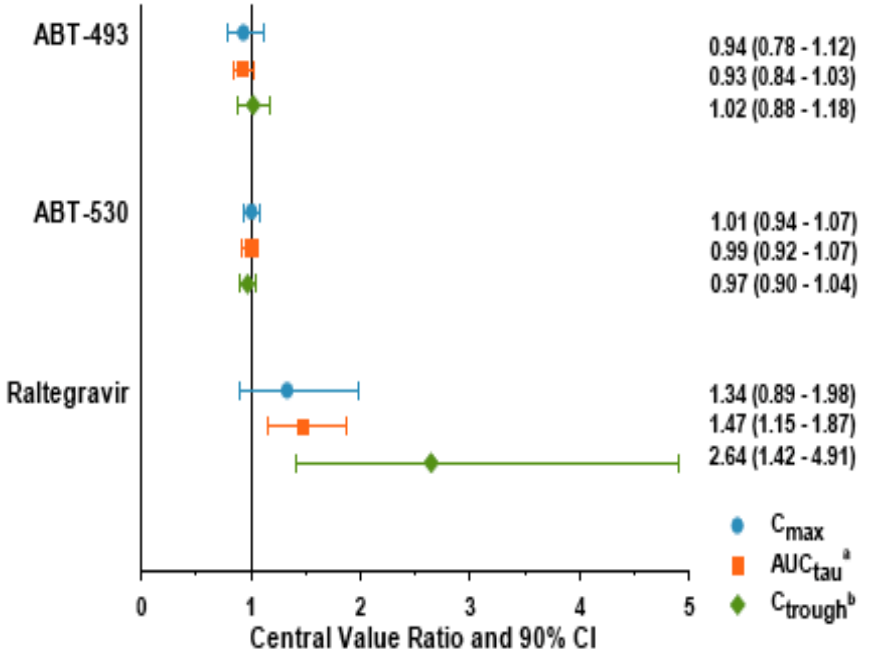


Figure 4. Interaction between ABT-493 and ABT-530 with Raltegravir (Central Value Ratios and 90% CIs)



ABT-493 and ABT-530: Period 2 Day 10 (Test)/Period 1 Day 7

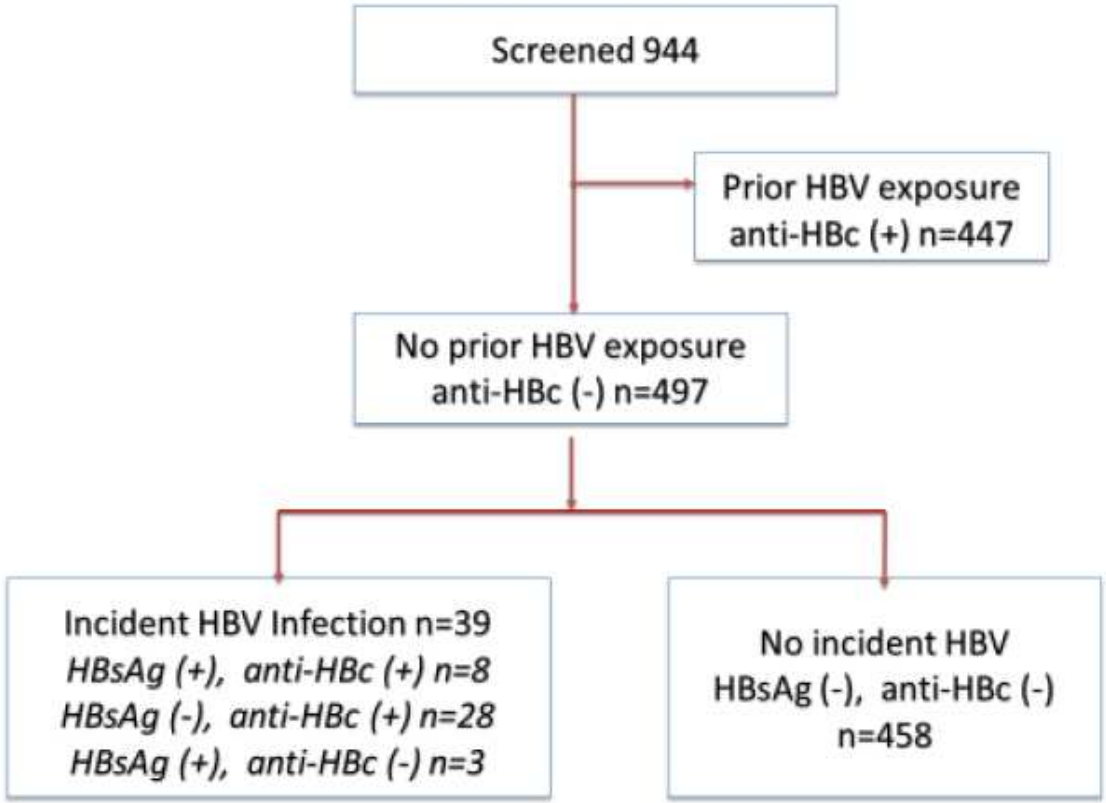
- ABT-493 and ABT-530 minimally effected by RPV or RAL
- Increased exposure of RAPV and RAL
- BUT modest increases and in line with label and other similar interactions so NO DOSE ADJUSTMENT required

New Drugs and DDIs – take home messages

- Pan-genotypic regimens (SOF+VEL and ABT-493+ABT-530)
- Few DDIs
  - SOF + VEL acceptable with TDF/TAF/boosted-PIs/RPV and INSTIs
  - ABT-493 + ABT-530 acceptable with RPV/RAL
- Phase 3 studies in HIV/HCV underway

Risk factors for adult HBV acquisition in HIV-infected adults in Rakai, Uganda

Figure 1: participant selection



Factors associated with HBV infection

Table 2: Factors associated with incident hepatitis B disease

Characteristics			Unadjusted HRs		Adjusted HRs	
	Cases/ person years	Incidence/ 100 person years	95% CI	p-value	95% CI	p-value
Overall	39/3342	1.17				
Gender						
Female	30/2380	1.26	Ref		Ref	0.70
Male	9/962	0.94	0.74 (0.4-1.6)	0.43	0.86 (0.4-1.8)	
Age						
40+	6/1256	0.48	Ref		Ref	
30-39	22/1662	1.32	2.78 (1.1-6.9)	0.004	2.18 (0.9-5.4)	0.05
15-29	15/423	2.60	5.46 (2.0-14.8)		3.66 (1.3-10.2)	
On ART*						
No	29/1238	2.34	Ref		Ref	
Yes	10/2103	0.48	0.20 (0.1-0.4)	<0.001	0.24 (0.1-0.5)	<0.001
Sex partners in last year						
0	8/813	0.98	Ref			
1	25/2089	1.20	1.21(0.5-2.7)	0.83		
>=2	6/440	1.36	1.38 (0.5-4.0)			
CD4 Count**						
0-99	1/55	1.81	Ref			
100-250	3/213	1.41	0.77 (0.1-7.4)	0.97		
251-499	12/740	1.62	0.89 (0.1-6.9)			
500+	12/903	1.33	0.74 (0.1-5.7)			

* Overall 287/497 initiated ART. At baseline, only 22 were on ART. Majority started ART in the observation period.

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3TC some protection, TDF no infections

Table 3: Association of ART regimen type with incident hepatitis B

Characteristics	HBV incidence		Unadjusted HRs		Adjusted HRs	
	Cases/person years (pys)	Incidence/100 pys (95% CI)	95% CI	p-value	95% CI	p-value
ART regimen						
No ART	29/1241	2.58(1.82-3.65)	Ref		Ref	
3TC	7/1243	0.89(0.49-1.60)	0.24(0.10-0.54)	0.001	0.29(0.13-0.69)	0.005
3TC and TDF	0/223	-	-	-	-	-
None 3TC/TDF	0/3.4	-	-	-	-	-

Study outcomes

- Thirty-nine new infections occurred over a period of 3,342 person years resulting in an incidence of 1.2 per 100 person years
- Overall, ART use was associated with a 76% reduction in incident HBV infection.
- No new HBV infection occurred among individuals that were on a tenofovir based ART regimen.
- Young adulthood (15-29 years) was associated with a high risk of incident HBV disease

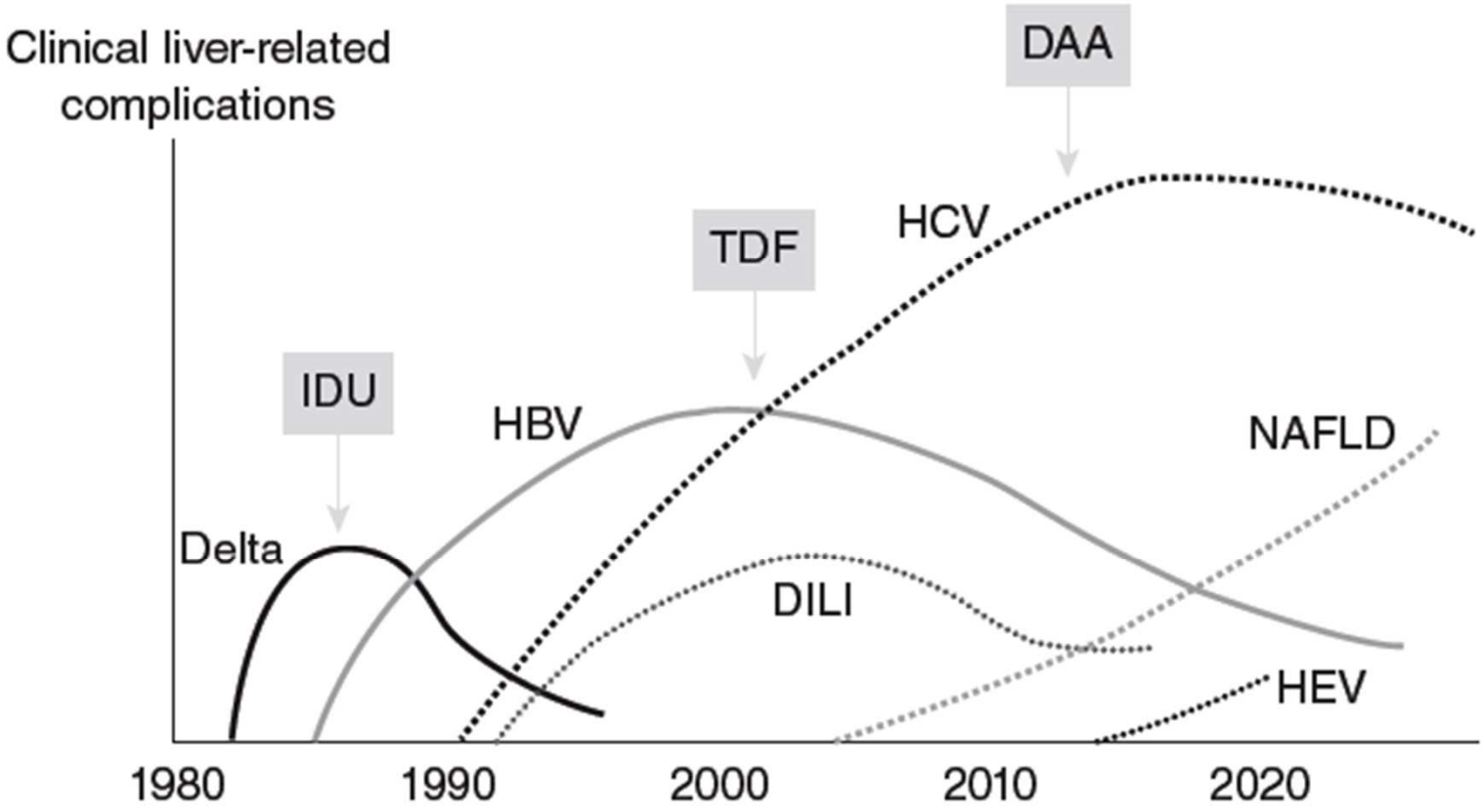
Limitations

- Convenience sample was used
- Some missing data

Conclusions

- HBV transmission occurs in adults in a country where this disease was thought to be primarily transmitted in childhood suggesting need for vaccine preventive strategies
- Our findings add to the growing body of knowledge that suggests that HBV active medications in an ART regimen offer prophylaxis against incident HBV.

And finally, what after HBV, HCV and HIV in terms of liver disease?



Soriano, et al, AIDS Review 2013; 15: 25-31

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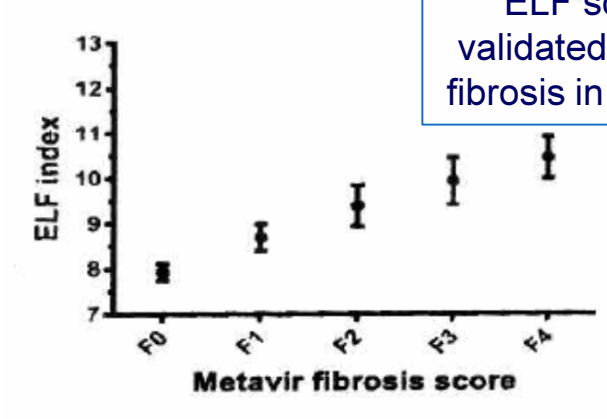
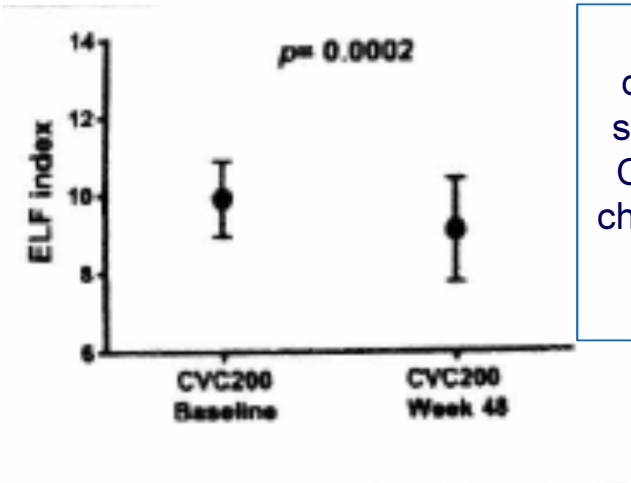
Antifibrotic effect of Cenicriviroc (CVC):

- Phase 2b study, pts with CCR5 trophic virus randomised to receive 100mg CVC, 200mg CVC or EFV in combination with TDF/FTC.



ELF score has been validated as a measure of fibrosis in NASH, HIV, HBV

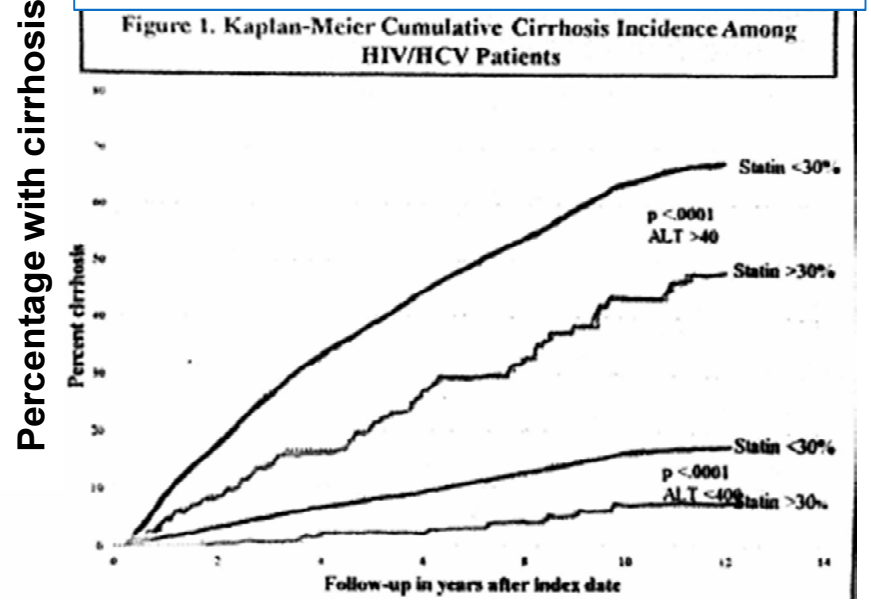


Significant decline in ELF score in 200mg CVC group, no change in 100mg CVC or EFV group

Statin use is Associated with decreased incidence of Cirrhosis

- US Veterans cohort HIV/HCV n=5985
- Evaluated time on statin and risk of incident cirrhosis

Significantly lower incidence of cirrhosis in those on statin>30% FU time



- In multivariate analysis, this effect was not significant in those with ALT>40 (thought to be due to low rates statin prescription in this group) but in those with ALT<40, statin was protective

Statin Therapy Reduces Liver Fat measured by CT in HIV+ patients

Methods

Study Design

- 12-month, randomized, placebo-controlled trial of atorvastatin in 40 men and women with HIV*

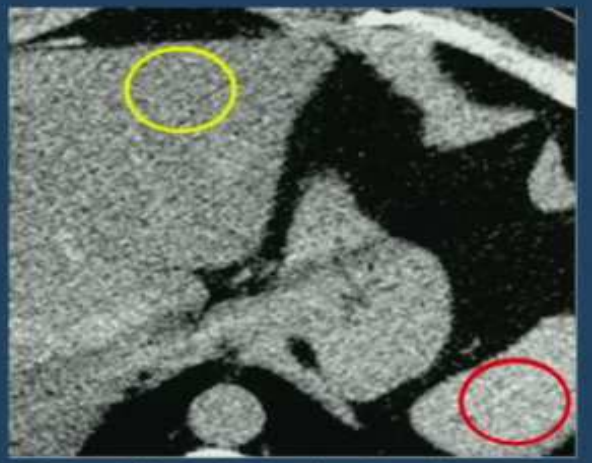
Enrollment Criteria

- No clinical CVD
- Stable ART > 6 months
- LDL (calculated) 70-130 mg/dL
- Excluded AST or ALT > 3x ULN or decompensated liver disease

*previously reported Lo et al. *Lancet HIV* 2015; CROI 2015

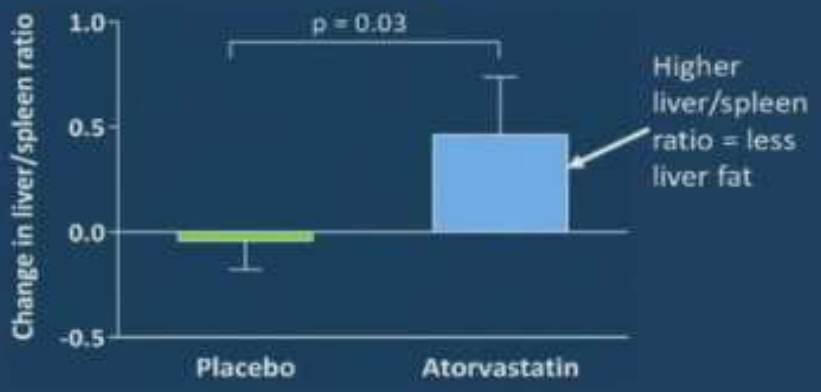
CT Methods

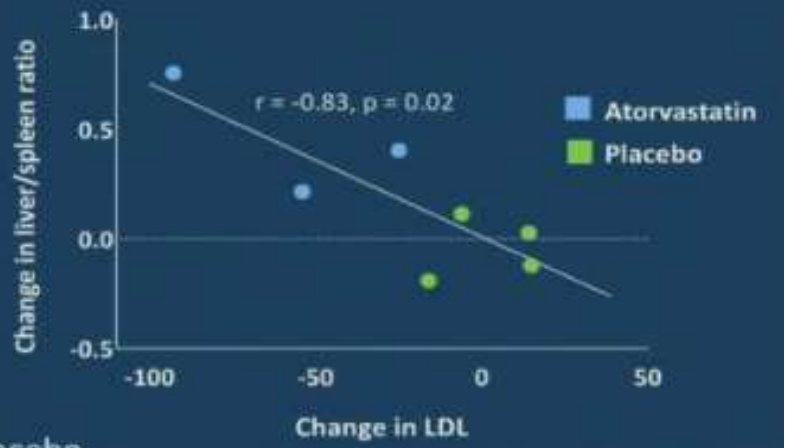
- Liver and spleen attenuation measured in Hounsfield Units using non-contrast CT
- Images read by blinded radiologist: 3 ROI's at 3 levels in liver and spleen
- NAFLD defined as a liver-to-spleen attenuation ratio < 1 correlates well with histological macrovesicular steatosis
- 9 participants had NAFLD



CT image of liver and spleen in patient with NAFLD

Among those with NAFLD, change over 12-months:





- Mean change in BMI and VAT similar in atorvastatin vs. placebo

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