Clinical case
HIV HCV coinfection

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PHC, January 2016

Disclosures

- Board of experts for Gilead and BMS

Objectives

- To discuss:
  - Results of DAA combination in HIV-HCV coinfection
  - Drugs-drugs interactions
  - Failures
  - Reinfections

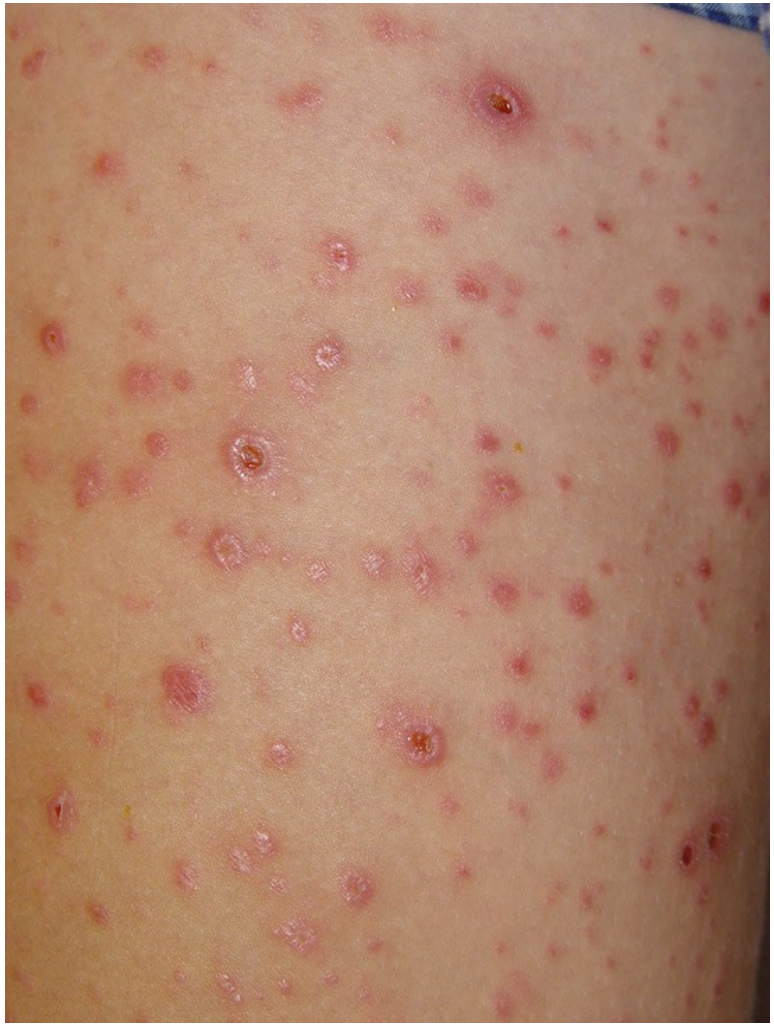
Clinical case 1

- Didier is a 36 year-old man, business manager in a company of special events.

- In 2011, a rectal abcess leads to the detection of an HCV positive serology (no previous test)
  - G1a
  - HCV RNA : 3 450 601 UI/ml (6,54 log)
  - Elastometry: 4,9 kPa
  - ALT normal
  - HIV negative

  No treatment decided

In January, apparition of a skin rash



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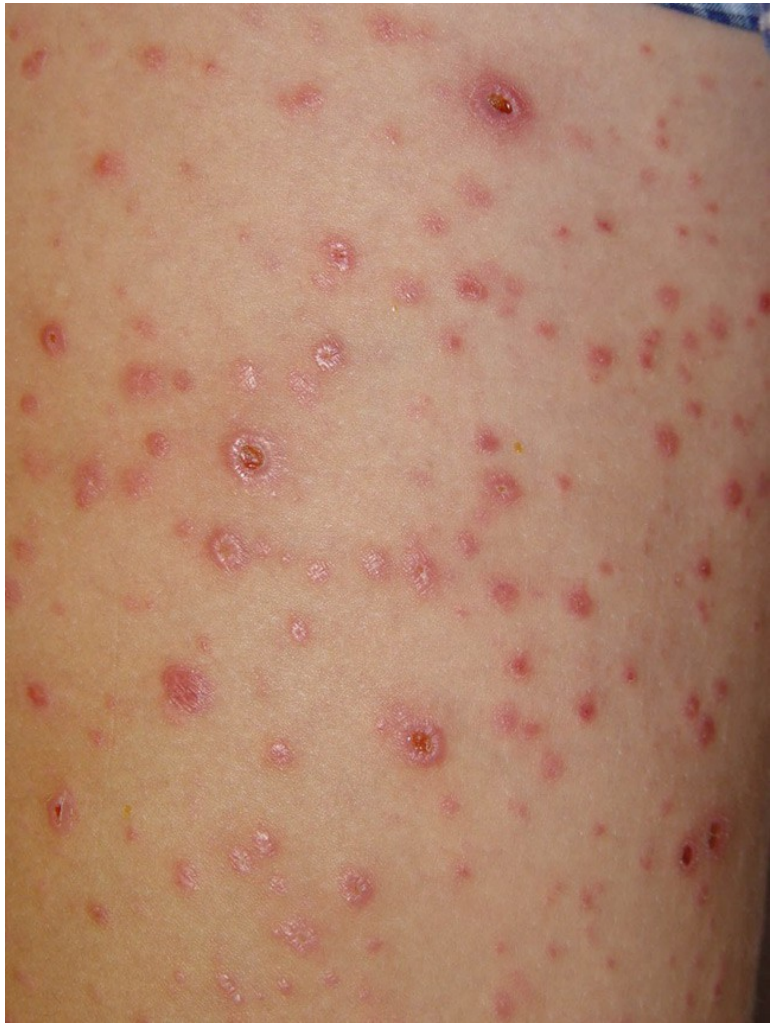
In January 2013, apparition of a skin rash



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Syphilides
ELISA+
VDRL : 32
UI

HIV acute infection

HIV disease

- Uncomplete HIV Western Blot
- CD4 : 388/mm3 - HIV RNA : 980.000 cop/ml
- Genotyping : HIV strain resistant to three classes
  - NVP and EFV
  - IDV and NFV
  - AZT and D4T
  - CCR5 tropism
- HLA B57*01 negative
- HAART was begun on January 24, 2013

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HIV disease

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  - AZT and D4T
  - CCR5 tropism
- HLA B57*01 negative
- HAART begun on January 24, 2013
  - tenofovir/lamivudine/raltegravir
  - switched in 2014 to tenofovir/lamivudine/dolutegravir

- We learned that
  - he his a sex addict and has bank problems (since he lost both parents at young age)
  - No tobacco nor drug usen but alcohol

- In June 2015 :
  - CD4: 490/mm3, HIV RNA < 20 cop/ml (few blips)
  - Creatinine : 117 µmol/l , clearance MDRD : 65 ml/mm
  - Weight : 72 kg
  - Treatment with rosuvastatin 10 mg/d
  - HCV RNA still positive, FS: 5.9 KPa

=> Decision to treat HCV + psychological support

What are the options giving more than 90% SVR rate in G1 HIV/HCV coinfection ?

Similar efficacy of all DAA regimens in HIV/HCV coinfection and between HIV/HCV and HCV infection

Natural history and treatment of HCV/HIV coinfection: Is it time to change paradigms?

Joop E. Arends[1,*,†], Faydra I. Lieveld[1], Lauke L. Boeijen[1], Clara T.M.M. de Kanter[2],

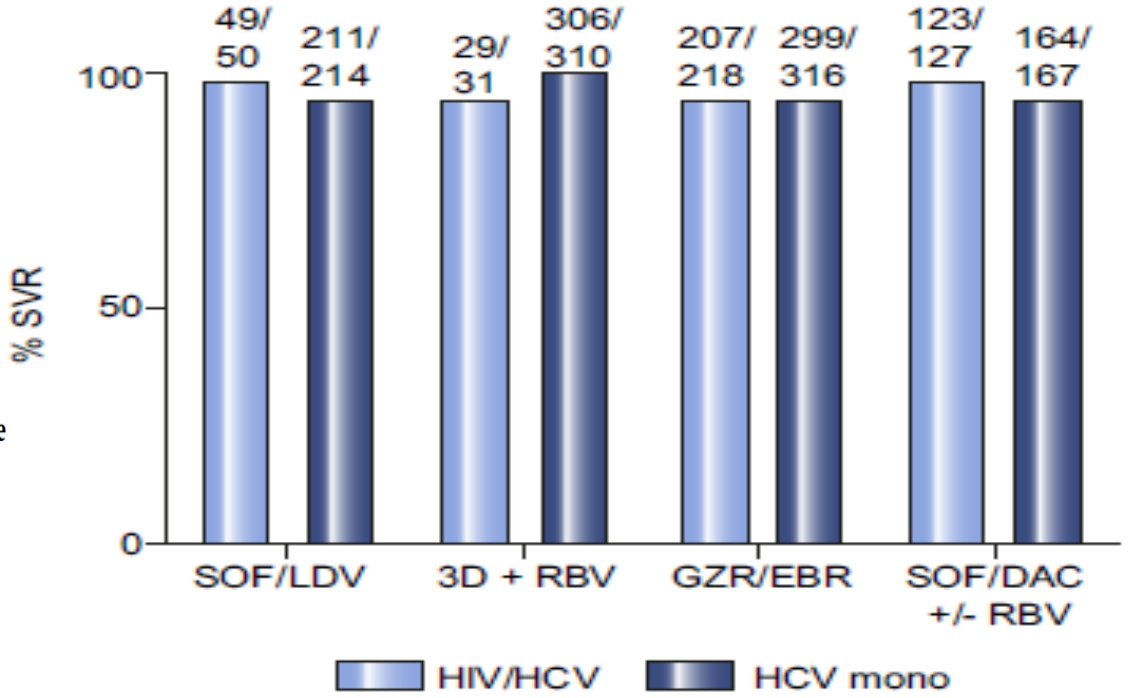
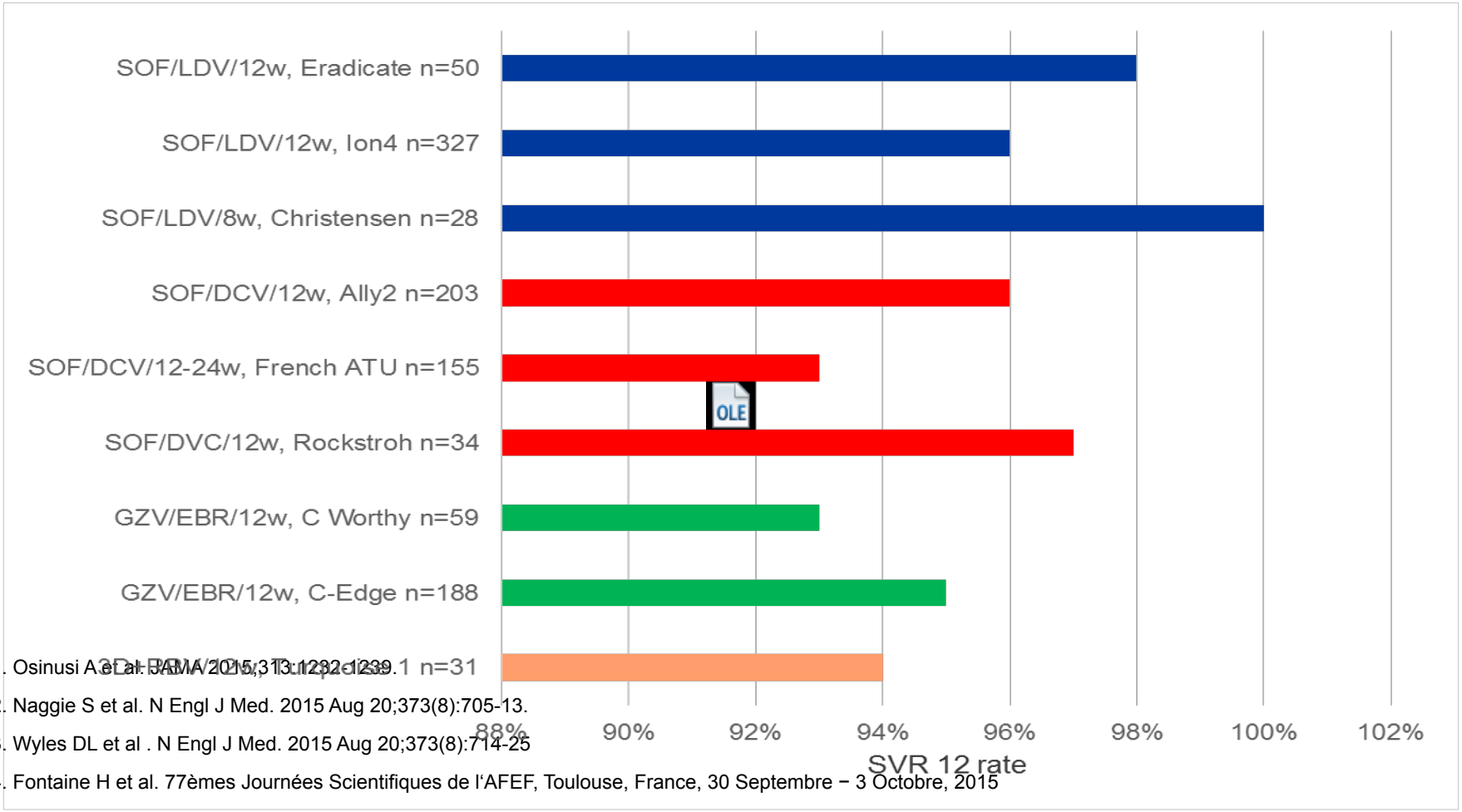


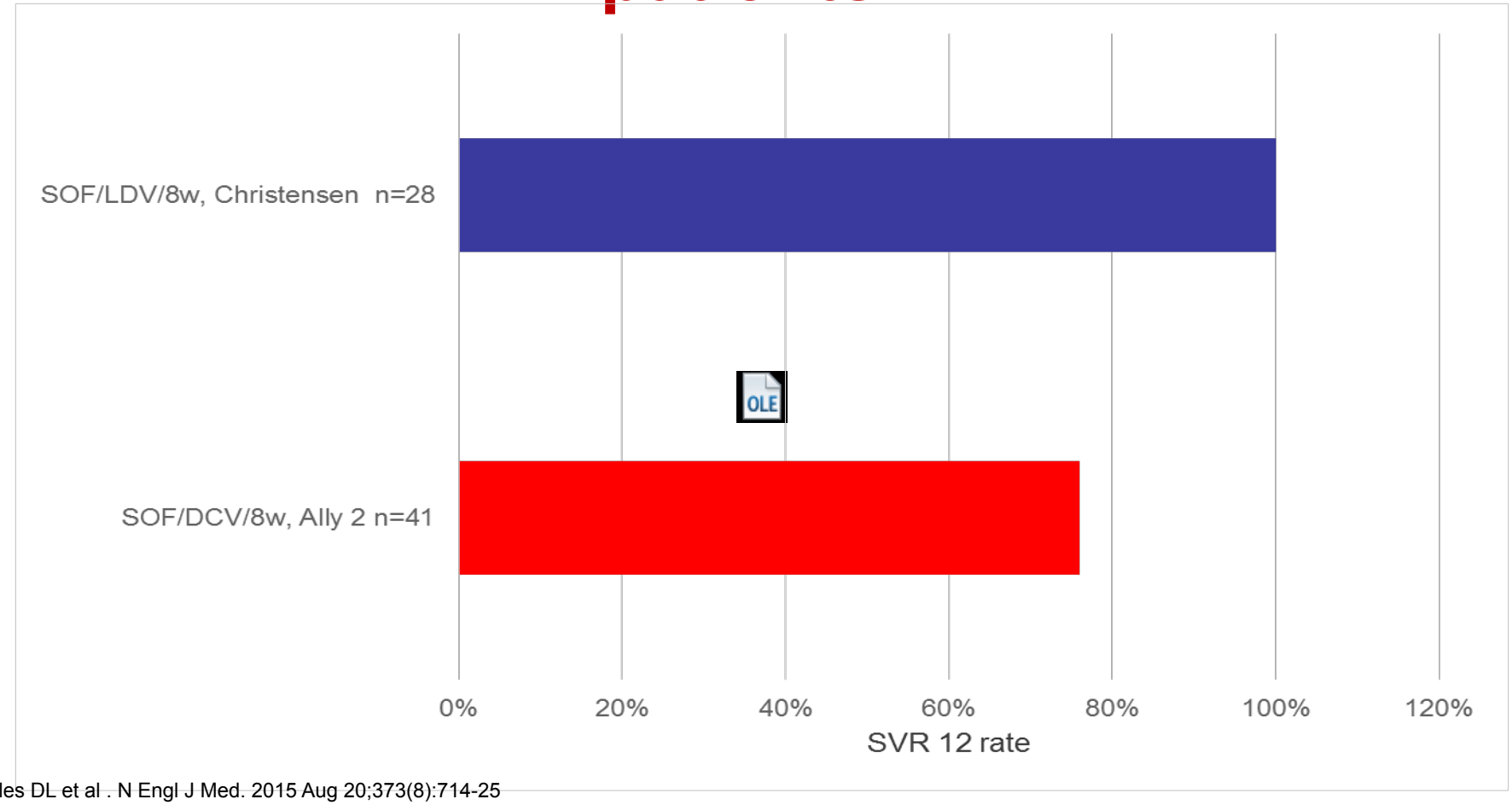
Fig. 1. SVR12 rates in IFN-free DAA studies in HIV/HCV co-infected patients with comparator data for HCV mono-infected patients. Studies included solely or mostly HCV genotype 1 patients. HIV/HCV coinfected patients are depicted in light blue bars and the HCV mono-infected patients in dark blue bars. Depicted studies are: SOF/LDV – ION-4 [31] and ION-1 [116]; 3D+RBV – Turquoise-1 [33] and PEARL-III and PEARL-IV [117]; GZR/EBR – C-EDGE COINFECTION [34] and C-EDGE [118]. SOF, sofosbuvir; LDV, ledipasvir; 3D, paritaprevir/ritonavir/ombitasvir/dasabuvir; RBV, ribavirin; GZR, grazoprevir; EBR, elbasvir; DAC, daclatasvir.

Options with a SVR rate > 90% in genotype 1 in HIV/HCV coinfection



- 1. Osinusi A et al. JAMA 2015;313:1232-1239.
- 2. Naggie S et al. N Engl J Med. 2015 Aug 20;373(8):705-13.
- 3. Wyles DL et al . N Engl J Med. 2015 Aug 20;373(8):714-25
- 4. Fontaine H et al. 77èmes Journées Scientifiques de l'AFEF, Toulouse, France, 30 Septembre − 3 Octobre, 2015
- 5. Rockstroh JK et al. Lancet HIV. 2015 Aug;2(8):e319-27.
- 6. C Worthy
- 7. Sulkowski MS, JAMA 2015;313:1223-1231.
- 7- Ingiliz P. 8 weeks. 5th European AIDS Conference October 21 - 24, 2015 Barcelona, Spain

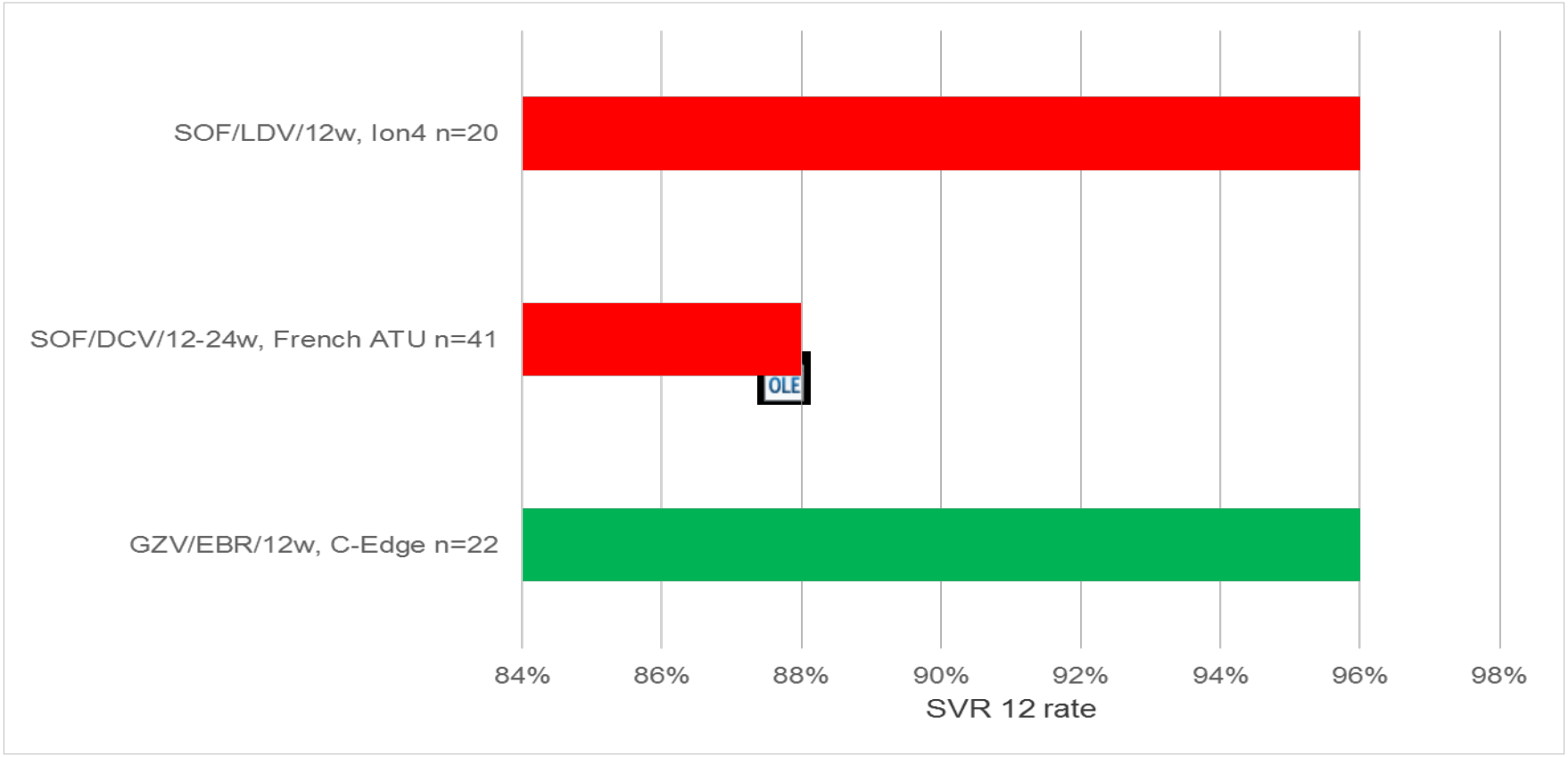
Genotype 1 in HIV/HCV coinfection : is 8 weeks a possible option for naïve patients?



Wyles DL et al . N Engl J Med. 2015 Aug 20;373(8):714-25

Christensen S, al. Sofosbuvir and ledipasvir for 8 weeks in patients with hepatitis C virus (HCV) mono-infection and human immunodeficiency virus (HIV)-HCV co-infection with genotype 1 and 4 in clinical practice – Results from the GErman hepatitis C COhort (GECCO)- A1081 AASLD 2015

Options with a SVR rate > 90% in genotype 4 in HIV/HCV coinfection

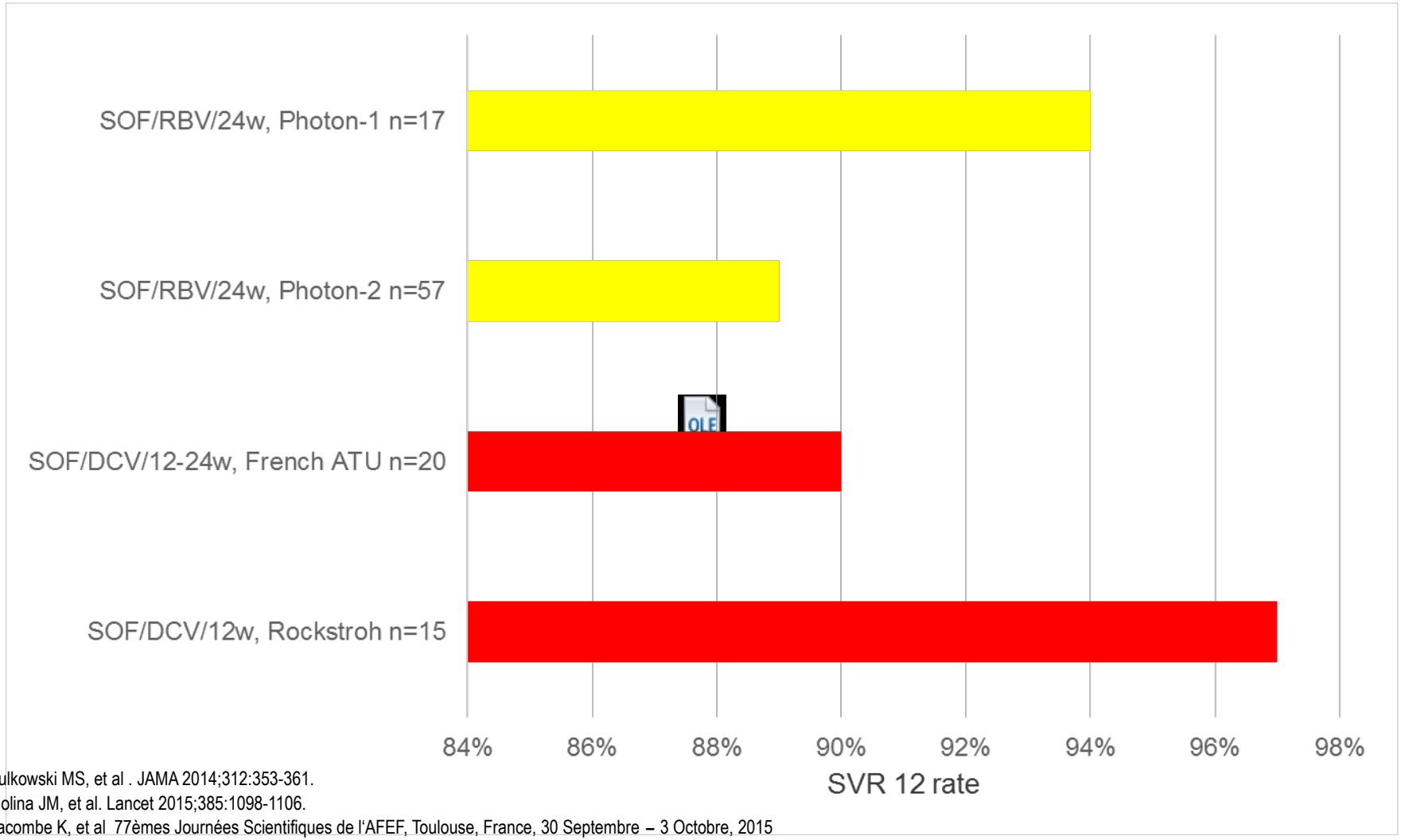


- Naggie S et al. N Engl J Med. 2015 Aug 20;373(8):705-13.

Fontaine H et al. 77èmes Journées Scientifiques de l'AFEF, Toulouse, France, 30 Septembre − 3 Octobre, 2015

Rockstroh JK et al. Lancet HIV. 2015 Aug;2(8):e319-27.

Options with a SVR rate > 90% in genotype 3 in HIV/HCV coinfection



Sulkowski MS, et al . JAMA 2014;312:353-361.
Molina JM, et al. Lancet 2015;385:1098-1106.
Lacombe K, et al 77èmes Journées Scientifiques de l'AFEF, Toulouse, France, 30 Septembre – 3 Octobre, 2015
Rockstroh J et al. A1058, AASLD 2015

Does his background treatment need to be optimized?

Truvada

Dolutegravir

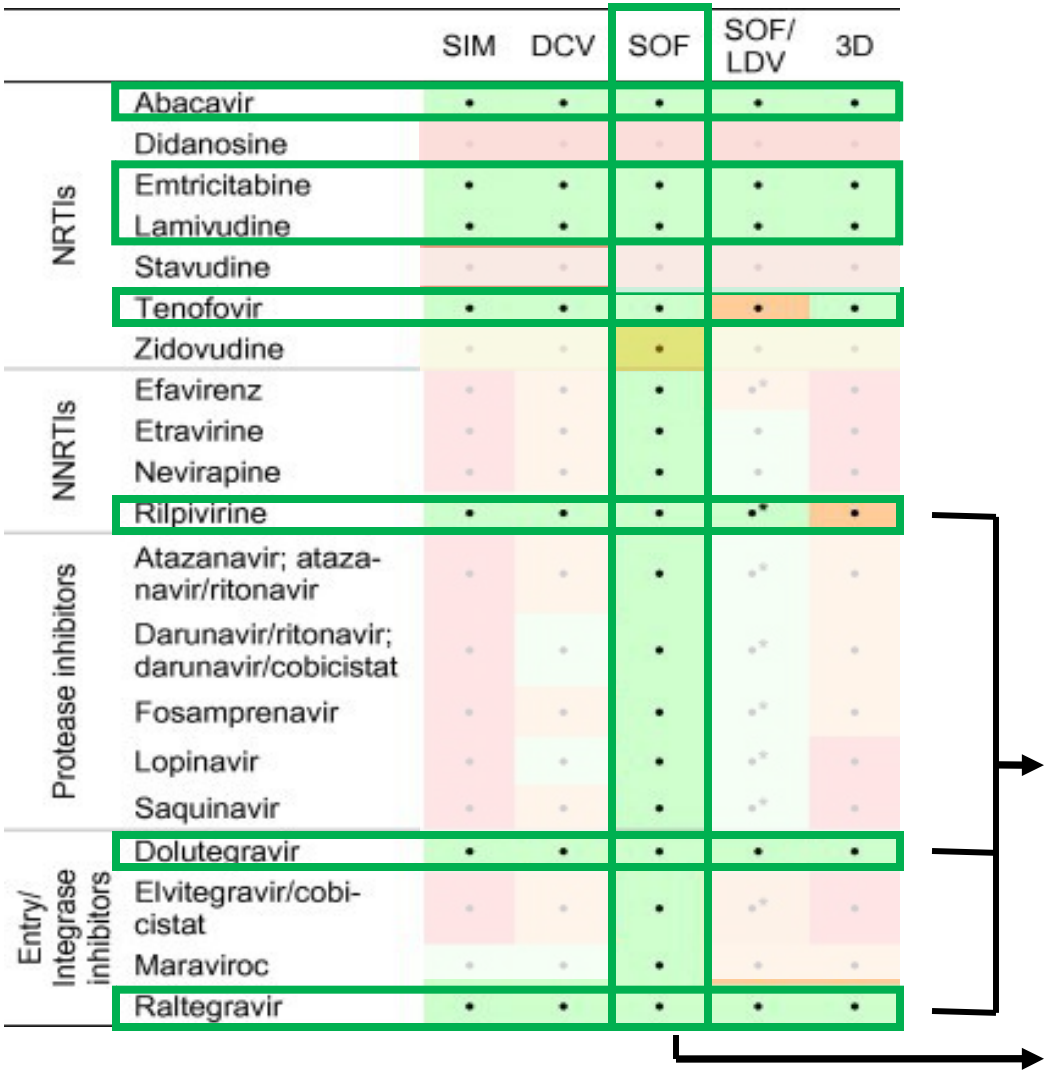
Rosuvastatine

Drug-drug interactions

		SIM	DCV	SOF	SOF/ LDV	3D
NRTIs	Abacavir	•	•	•	•	•
	Didanosine	•	•	•	•	•
	Emtricitabine	•	•	•	•	•
	Lamivudine	•	•	•	•	•
	Stavudine	•	•	•	•	•
	Tenofovir	•	•	•	•	•
	Zidovudine	•	•	•	•	•
NNRTIs	Efavirenz	•	•	•	•*	•
	Etravirine	•	•	•	•	•
	Nevirapine	•	•	•	•	•
	Rilpivirine	•	•	•	•*	•
Protease inhibitors	Atazanavir; atazanavir/ritonavir	•	•	•	•*	•
	Darunavir/ritonavir; darunavir/cobicistat	•	•	•	•*	•
	Fosamprenavir	•	•	•	•*	•
	Lopinavir	•	•	•	•*	•
	Saquinavir	•	•	•	•*	•
Entry/ Integrase inhibitors	Dolutegravir	•	•	•	•	•
	Elvitegravir/cobicistat	•	•	•	•*	•
	Maraviroc	•	•	•	•	•
	Raltegravir	•	•	•	•	•

EASL recommandations 2015

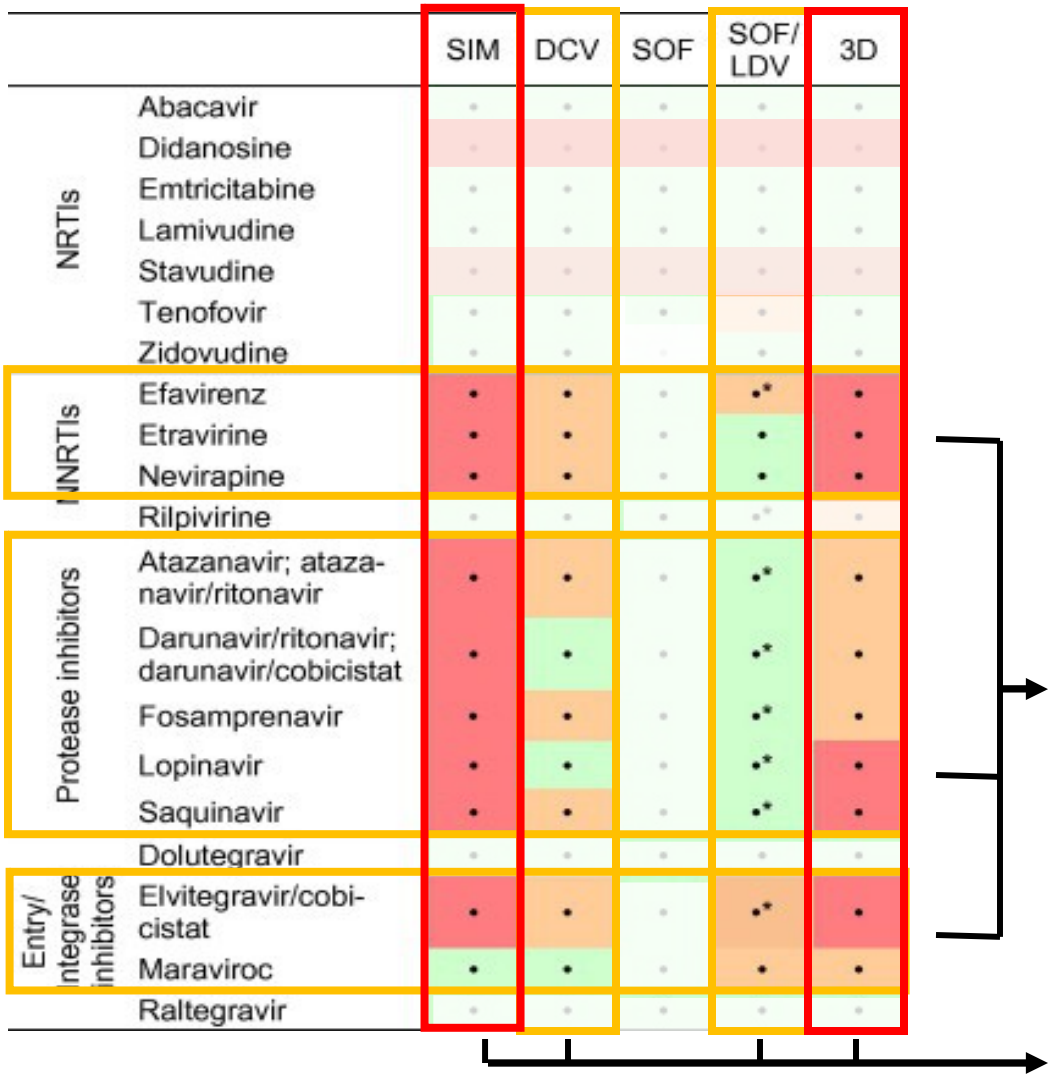
Drug-drug interactions



- We have to think in both directions!

← simple = everything sticks perfectly

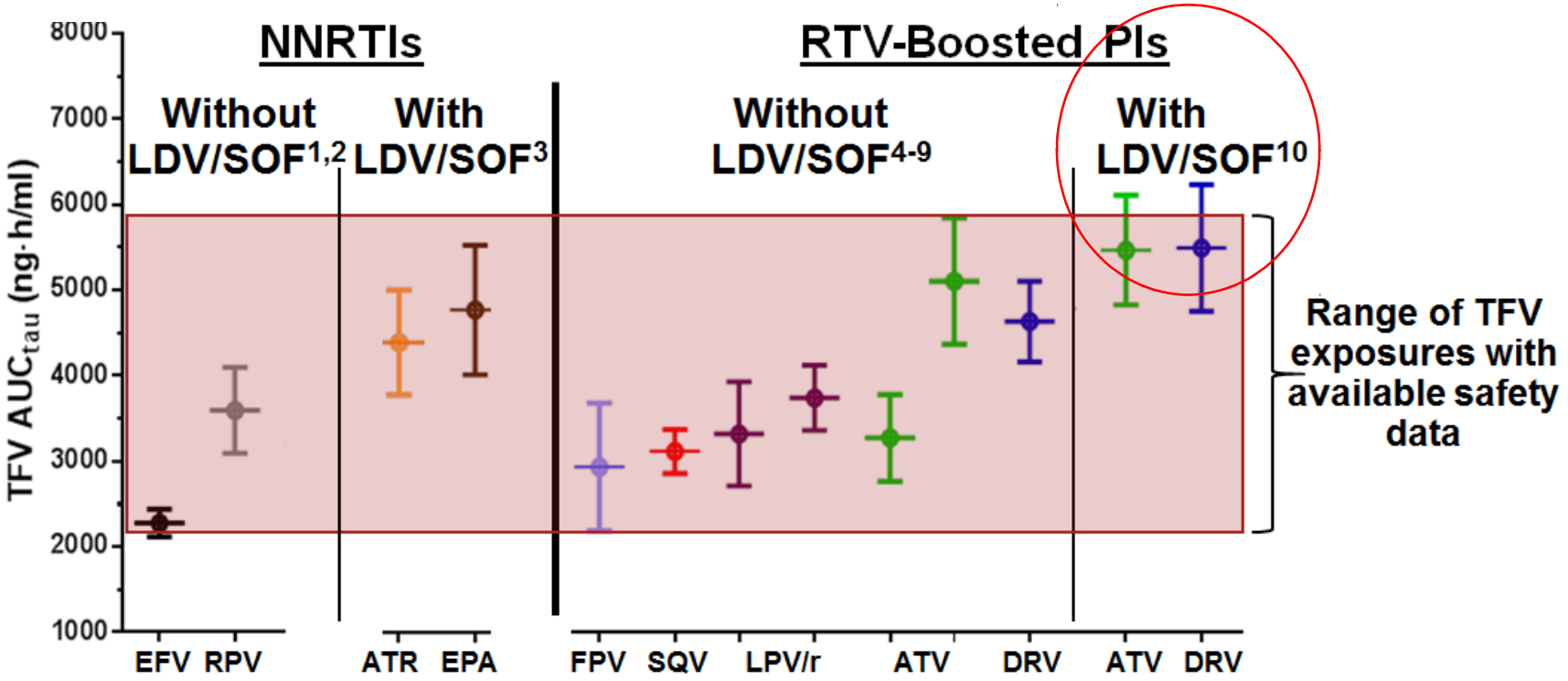
Drug-drug interactions



- We have to think in both directions!

➔Adapt HIV or HCV treatment ….

Influence of LDV/SOF on TDF PK



⇒ 30-60% increase of TDF exposition in the presence of ledipasvir/ sofosbuvir + boosted PI

- **Monitor for tenofovir adverse events during coadministration with any TDF-based regimen**

1, Data on File, Gilead Sciences.
2. Hoetelmans RMW, et al. 6th IWCPHT 2005. Quebec City, Canada. Poster #2.11
3. German P, et al. ICPHHT 2014. #O6
4. Luber AD, et al. *HIV Medicine*. 2010;11:193-9 (FPV + RTV)
5. Chittick GE, et al. *AAC*. 2006; 50(4):1304-10 (SQV + RTV)
6. Zhu L, et al. 9th IWCPHT 2008. #023 (ATV+RTV & LPV/r)
7. Kearney B, et al. *JAIDS*. 2006;43(3):278-83 (LPV/r)
8. Agarwala S, et al. 6th IWCPHT 2005. #16. (ATV + RTV)
9. Hoetelmans RMW, et al. *BJCP*. 2007;64(5):655-61 (DRV + RTV)
10. German P, et al. CROI 2015. Oral #82 (ATV + RTV and DRV + RTV)

* HIV-infected subjects

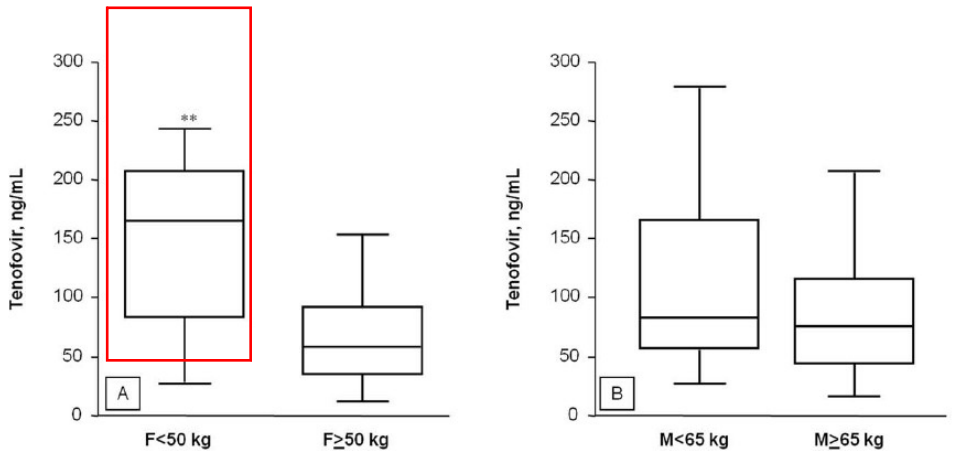
Demographic data et plasma TDF Cmin

TABLE 3. Multivariate Analysis of Factors Associated With GFR Changes at the Time of TDF Concentration Determination

	Men		Women	
Variable	Coefficient	*P*	Coefficient	*P*
Age	−0.865	0.001	−1.043	0.03
BMI	1.726	0.028	1.552	0.18
BL-GFR	−0.313	0.007	−0.489	0.01
CTrough-TDF >90 ng/mL	−3.201	0.475	−15.307	0.02
Hypertension	−1.946	0.734	20.657	0.18
Diabetes	−1.346	0.833	14.946	0.22
HCV–PCR+	2.481	0.623	13.274	0.08
PI/r	0.399	0.932	−13.109	0.11
ATV	−4.105	0.364	−6.830	0.37

(Poizot-Martin I et al., JAIDS 2013)

Figure 2. TDF plasma trough concentrations measured female (panel A) and male (panel B) HIV infected patients stratified according to median body weight (**p<0.01).



(Gervasoni C et al., Plos one 2013)

- Increase risk of risk of renal clearance changes with tenofovir if
- Plasma TDV Cmin (C24h) > 90 ng/ml

⇒ • Do not give LDV/SOF if TRUVADA + boosted PI
…..at least in female with low weight

Influence of LDV/SOF on TDF PK

EASL recommandations 2015

The fixed-dose combination of sofosbuvir and ledipasvir can be used with all antiretrovirals. However, this regimen should not be used with the combination of tenofovir/emtricitabine with atazanavir/ritonavir, darunavir/ritonavir, lopinavir/ritonavir or elvitegravir/ cobicistat when possible, or used with caution with frequent renal monitoring **(B1)**

AASLD recommandations AASLD

Because ledipasvir increases tenofovir levels, concomitant use mandates consideration of creatinine clearance (CrCl) rate and should be avoided in those with CrCl below 60 mL/min. Because potentiation of this effect is expected when tenofovir is used with ritonavir-boosted HIV protease inhibitors, ledipasvir should be avoided with this combination (pending further data) unless antiretroviral regimen cannot be changed and the urgency of treatment is high.

Rating: Class IIa, Level C

Fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) (hereafter ledipasvir/sofosbuvir) should NOT be used with cobicistat and elvitegravir, pending further data.

Rating: Class III, Level C

⇒ **Recommandations**

- **EASL : LDV/SOF + TDF/IP/r or ELV/co : use with caution,creat measure**
- **US : do not use LDV/SOF with TDF/IP/r or ELV/cob**

Drug-drug interactions

- Be aware of the numerous co-prescriptions
  - Ex : 18% of HIV HCV patients receive a statin 30% VIH+

Bedimo HIV Med 2010

Without forgetting

	SIM	DCV	SOF	SOF/ LDV	3D
Atorvastatin	•	•	•	•	•
Bezafibrate	•	•	•	•	•
Ezetimibe	•	•	•	•	•
Fenofibrate	•	•	•	•	•
Fluvastatin	•	•	•	•	•
Gemfibrozil	•	•	•	•	•
Lovastatin	•	•	•	•	•
Pitavastatin	•	•	•	•	•
Pravastatin	•	•	•	•	•
Rosuvastatin	•	•	•	•	•
Simvastatin	•	•	•	•	•

	SIM	DCV	SOF	SOF/ LDV	3D
Amphetamine	•	•	•	•	•
Cannabis	•	•	•	•	•
Cocaine	•	•	•	•	•
Diamorphine	•	•	•	•	•
Diazepam	•	•	•	•	•
Gamma-hy-droxybutyrate	•	•	•	•	•
Ketamine	•	•	•	•	•
MDMA (ecstasy)	•	•	•	•	•
Methamphetamine	•	•	•	•	•
Phencyclidine (PCP)	•	•	•	•	•
Temazepam	•	•	•	•	•

EASL recommandations 2015

Table 2. Effects of HCV Agents on Transporter Substrates (HCV Agents as Perpetrators of Interactions)

	Digoxin (P-gp)		Pravastatin (OATP1B1/B3)		Rosuvastatin (OATP1B1/BCRP)	
	AUC	Cmax	AUC	Cmax	AUC	Cmax
ABT450/r/ombitasvir/dasabuvir	↑16%	↑15%	↑82%	↑37%	↑159%	↑613%
Asunaprevir	↑30%	↔	NP	NP	↑41%	↑95%
Daclatasvir	↑27%	↑65%	NP	NP	↑58%	↑104%
GS-5816	↑34%	↑88%	↑35%	↑28%	↑169%	↑161%
GS-9451/ledipasvir/tegobuvir	↑34%	NP	↑168%	↑166%	↑699%	↑1670%

AUC=area under the curve, Cmax=maximum concentration, NP=not presented

GS- 5816 : velpatasvir;
GS9451 : NS3 HCV NS3 P
Tegobuvir : NS5a polymerase inhibitor

www.HCV-drug interactions

Sofosbuvir/ledipasvir begun on July 1st, 2015

- HAART maintained : TDF/FTC/dolutegravir
- Rosuvastatin switched for pravastatin

- At month 1
  - HVC RNA < 12 detectable
  - Creatinin raised to 140 mmol/l, MRDR clearance 51 ml/mn

Course of the disease

- TDF decreased to 1 pill every 2 days

- Month 3: < 12 UI/mL detectable
- Month 4 : 14.374 UI/mL
- Month 4 : 17.851.00 UI/mL

Why this relapse ?
What to do now?

Predictors of failure in phase 3 trials of HIV-HCV coinfection

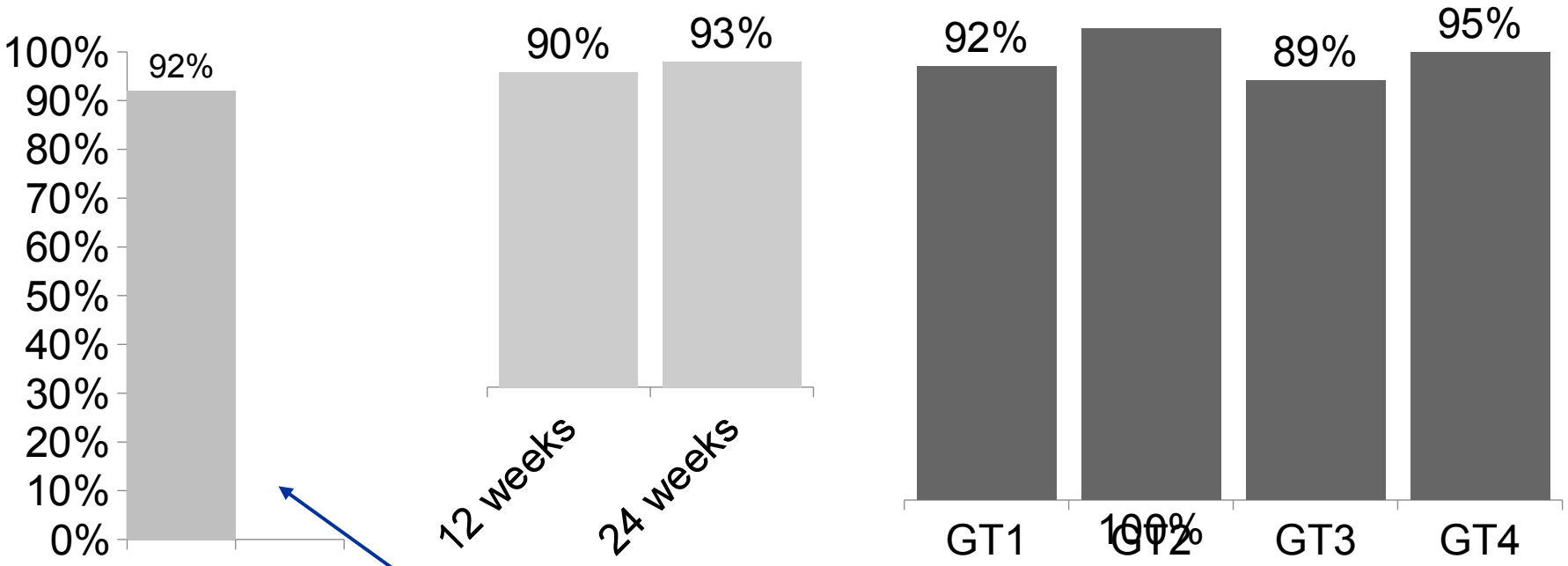
- Cirrhosis (OR=4.9, p=0.012, Photon 2)
- HCV RNA > 6 log (OR=34.4, p=0.02, Photon 2)
- Black race (OR =17.7, p=0.0012, Ion4)
- IL28B TT(OR=4,3, p=0.075, Ion4)

1.Molina JM et al , S et al. N Engl J Med. 2015 Aug 20;373(8):705-13.

2.Naggie S et al. N Engl J Med. 2015 Aug 20;373(8):705-13 .

Response to DAA regimen in real life ANRS CO 13 Hepavih Cohort - SVR12 (1)

215 patients ended an all-oral DAA regimen until 01/2015, SVR rate was 92% and 18 patients (8%)failed therapy



Relapse n = 15
Breaktrough n= 2
Death before SVR12 n=1

Rencontre Sainte Marguerite, October 2015; CROI 2016

Failure of DAA regimen in HIV/VHC coinfection : ANRS CO13 HEPAVIH Cohort (2)

Cirrhosis	**71%**
Child Pugh B	22%
Genotype 1/3/4 (%)	66%/ 17%/17%
CD4 cells/mm3, median	525
HIV RNA undetectable,(%)	64%
RBV (%)	43%
12 weeks duration planned (%)	43%
SOF+ DVC (n,%) *30 mg/60 mg/90 mg*	10 (57%) *6 /2/1*
SOF+RBV (n,%)	4 (22%)
SOF+LDV (n,%)	3 (17%)
SOF+SIM (n, %)	1 (5%)

Is it useful to detect RAVs?

What is the best technique?

When to do the test : baseline and/or at failure?

What is the impact on SVR?

Is the impact similar whatever the genotype?

Resistance associated mutations in HIV HCV coinfection trials

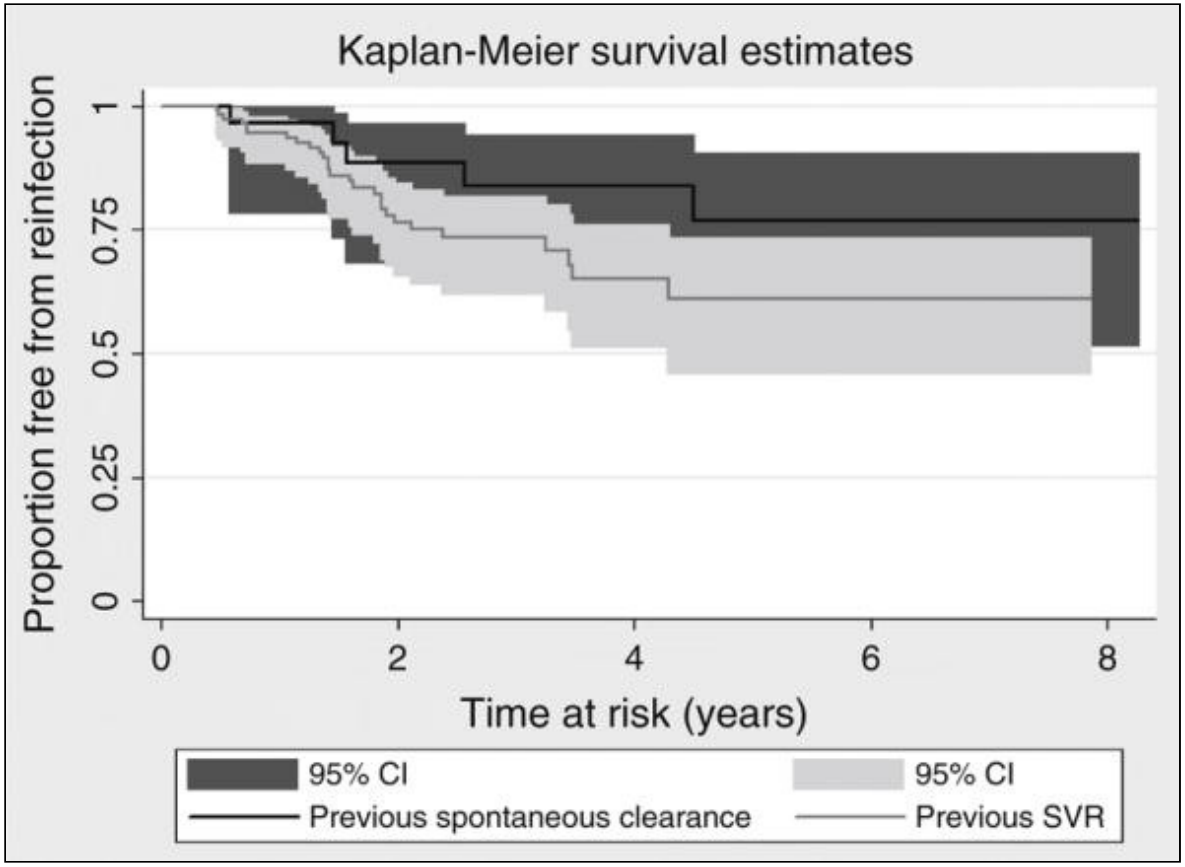
Study	Nb failures	RAVs to NS5A		RAVs to NS5B (S282T)
		Baseline	At failure	
Eradicate, SOF/LDV	1	Y93H (38%) ➔	Y93H (99%)	0
Ion 4, SOF/LDV	12	18% RAVs Similar SVR12 between RAVs+ and RAVs –	12/12 (100%) had RAVs emergence	0
Ally 2, SOF/DCV	39	17% RAVs (codon 28, 30, 31, or 93) Similar SVR12 between RAVs+ and RAVs-	2/12 relapses had new RAVs.	1/39 NS5B polymorphism (C316H+V321I).
Turquoise 1, 3D + RBV	2		2/2 had RAVs resistant to 3 classes	
Photon-2, SOF/RBV	31.			4/31 RAVS -2 low level (L159F, L159N + S282N + V321A) -2 high level RAVs (L159T) No variant S282T

Is there a reinfection ?

- In C-EDGE coinfection, among 8 failures, at least 2 patients had a new infection
  - Genotype 1a et 1b at baseline ➔ génotype 3.

5. Rockstroh JK et al. Lancet HIV. 2015 Aug;2(8):e319-27.

Rate of HCV reinfection after acute HCV hepatitis in MSM



- 191 HIV+ MSM with acute HCV
- 32 reinfections of 145 cases
  - 25% reinfection within 2 years
- 17 again treated or spontaneous clearance

Martin et al. AIDS Oct. 2013

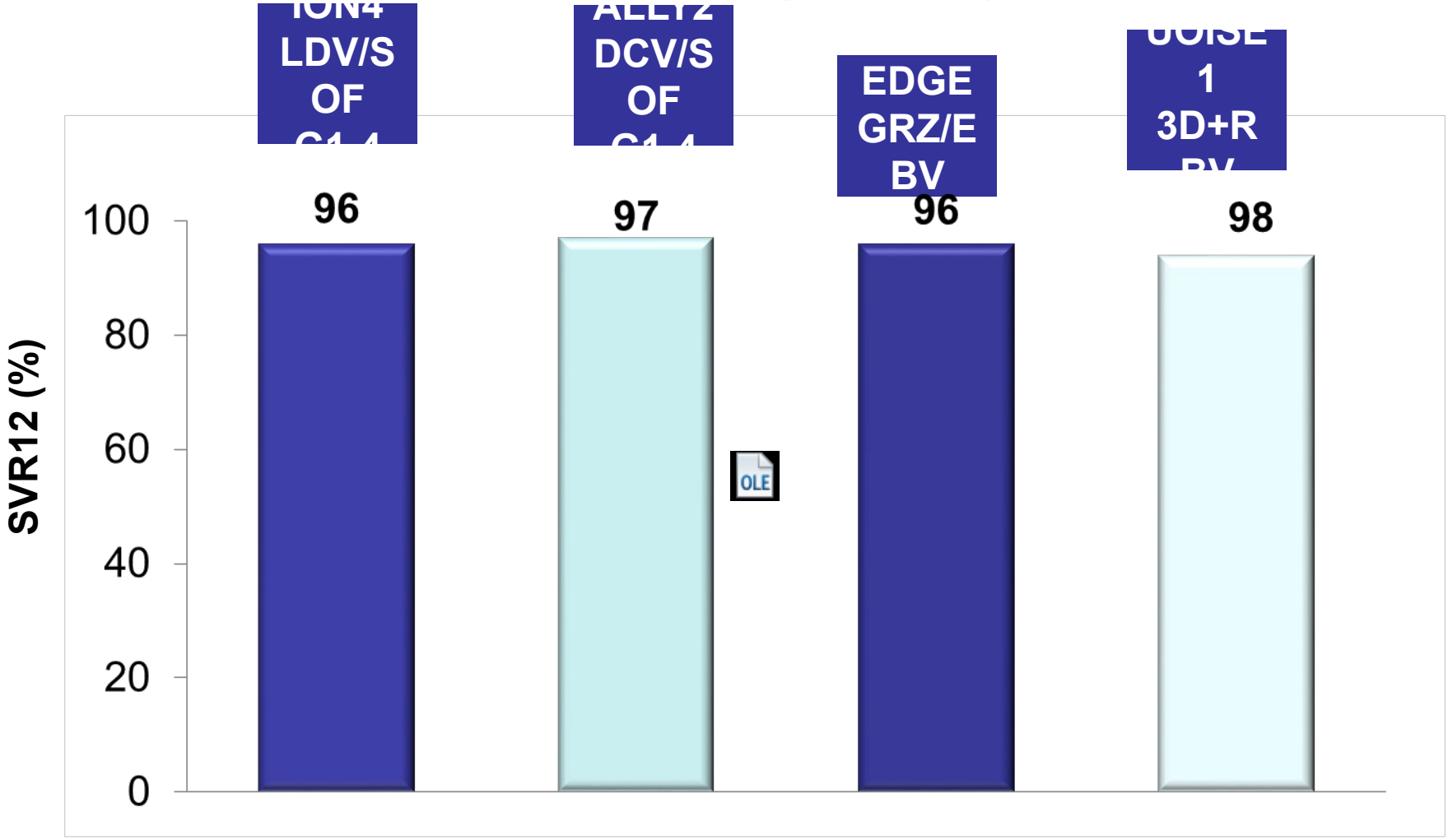
Conclusion

- Similar SVR rates than in HCV monoinfection
- Be aware of :
  - Drugs-drugs interactions
  - Compliance to therapy
  - HICV reinfection
- Usefulness to detect RAVs: to be further investigated

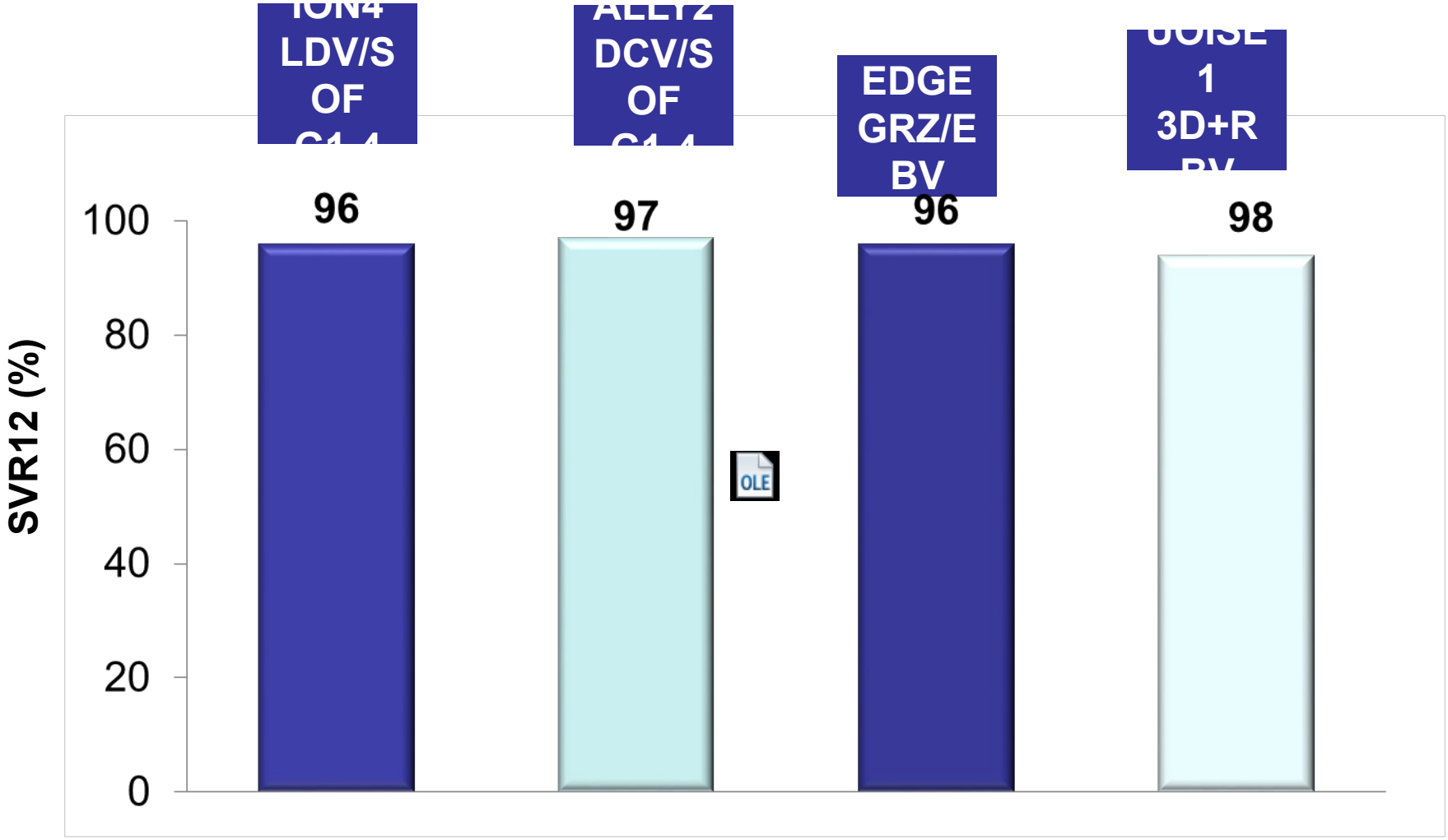
5. Rockstroh JK et al. Lancet HIV. 2015 Aug;2(8):e319-27.

BACK-UP

DDA 12 weeks trials in HCV/HIV Co-infection : all genotypes



DDA 12 weeks trials in HCV/HIV Co-infection : G4



DDA 12 weeks trials in HCV/HIV Co-infection : G1