HCV: The next 18 months…

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FIRST, A LOOK BACK…WHAT DID I SAY LAST YEAR?

My predictions for genotype 1:

- Multiple highly efficacious, well-tolerated, IFN-free genotype 1 regimens will be approved ✔
  - SOF+NS5A: no RBV; 8 weeks naïve, 12 weeks all others ±
    - SOF/DCV compassionate use right now in EU
  - SOF/PI: as efficacious; no phase 3 planned
  - PI-based regimen(s): RBV for some (1a); 12 weeks ±
    - Similar efficacy
      - Prior PI failures
    - Slightly more complex dosing
    - Drug interaction potential
- Almost no role for Interferon from a medical standpoint ✔?

Closing Remarks (2014)

- Progress on HCV antiviral continues at a remarkable pace
  - Multiple IFN-free regimens with >95% SVR rates will be approved for GT1
  - Promising option for difficult to treat GT3 cirrhotics exist…but more data is needed
- Resistance will not be major consideration
- Challenges facing us include diagnosis, access to care (providers), and resource allocation

Outline: The next 18 months

- Evolution of GT1 therapy…yawn.
  - Approval of additional regimens
- Non-genotype 1 and pangenotypic regimens
  - This is where the action is!
- The race to shorten therapy
  - Is it worthy of all the hype?
- Is resistance dead?
  - The emergence of NS5A resistance

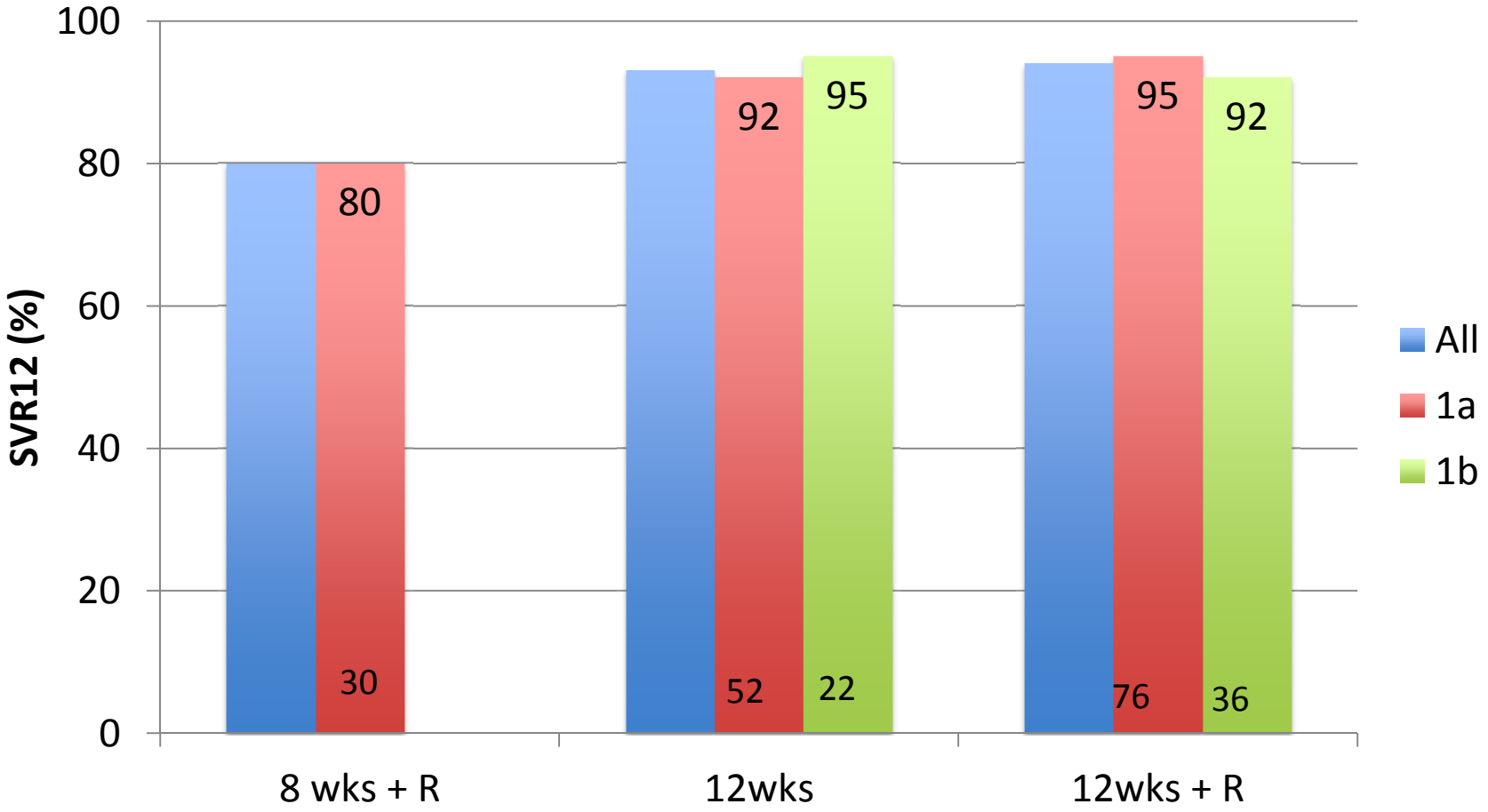
NEW REGIMENS FOR GENOTYPE 1

C-WORTHY Studies

- Grazoprevir- next generation NS3 PI
  - Enhanced pangenotypic activity
  - Higher resistance barrier
- Elbasvir- NS5A inhbitor
  - Potent, pangenotypic activity
- GZP 100mg + ELB 50mg +/- RBV
  - Non-cirrhotic: 8 wks vs 12 wks
    - 59% male, 88% white, 73% 1a, 8% F3
    - Included HIV co-infected subjects
  - Null and/or Cirrhosis: 12 wks vs 18 wks

Sulkowski MS. Lancet 2014. Lawitz E. Lancet 2014.

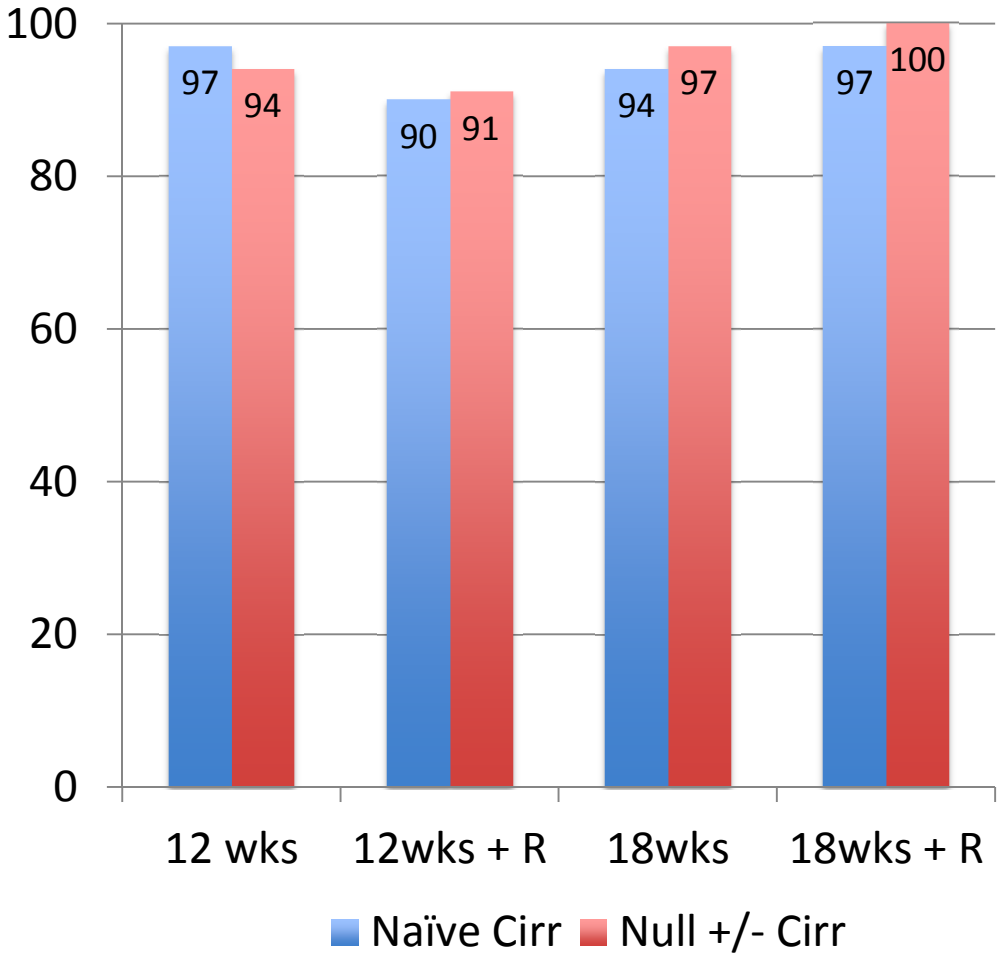
C-WORTHY Non-cirrhotic

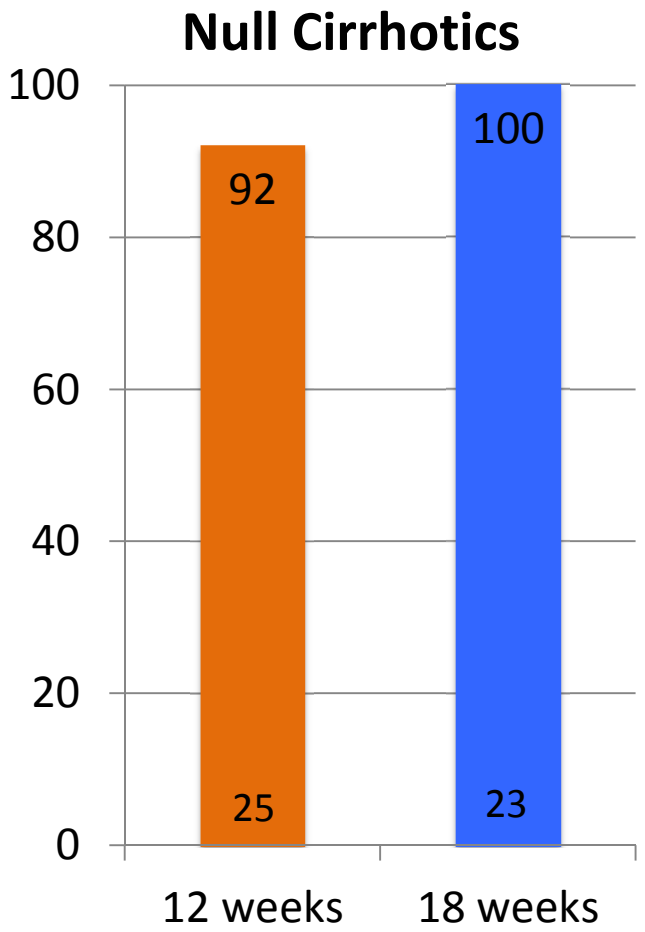


4% virologic failure rate in 12 week arms (7/188).

Sulkowski MS. Lancet 2014.

C-WORTHY Difficult to treat populations

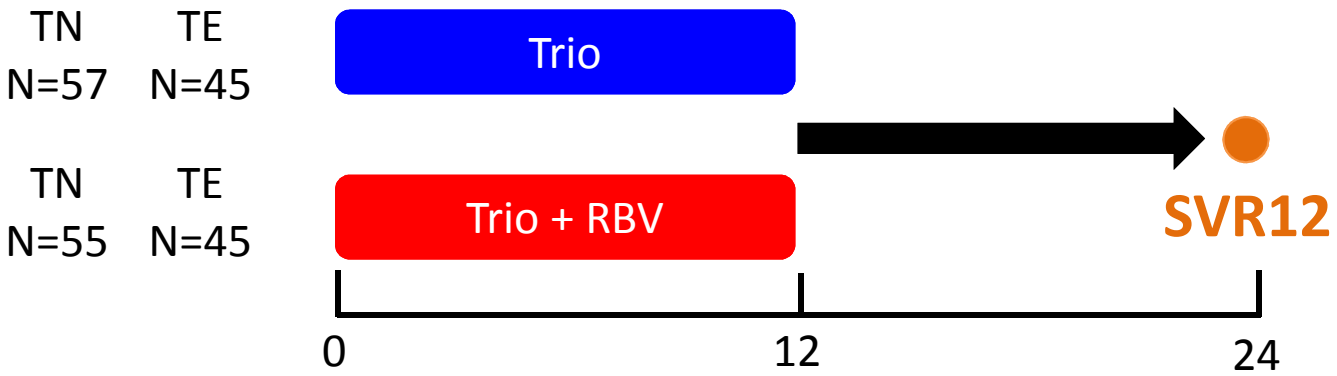




Lawitz E. Lancet 2014.

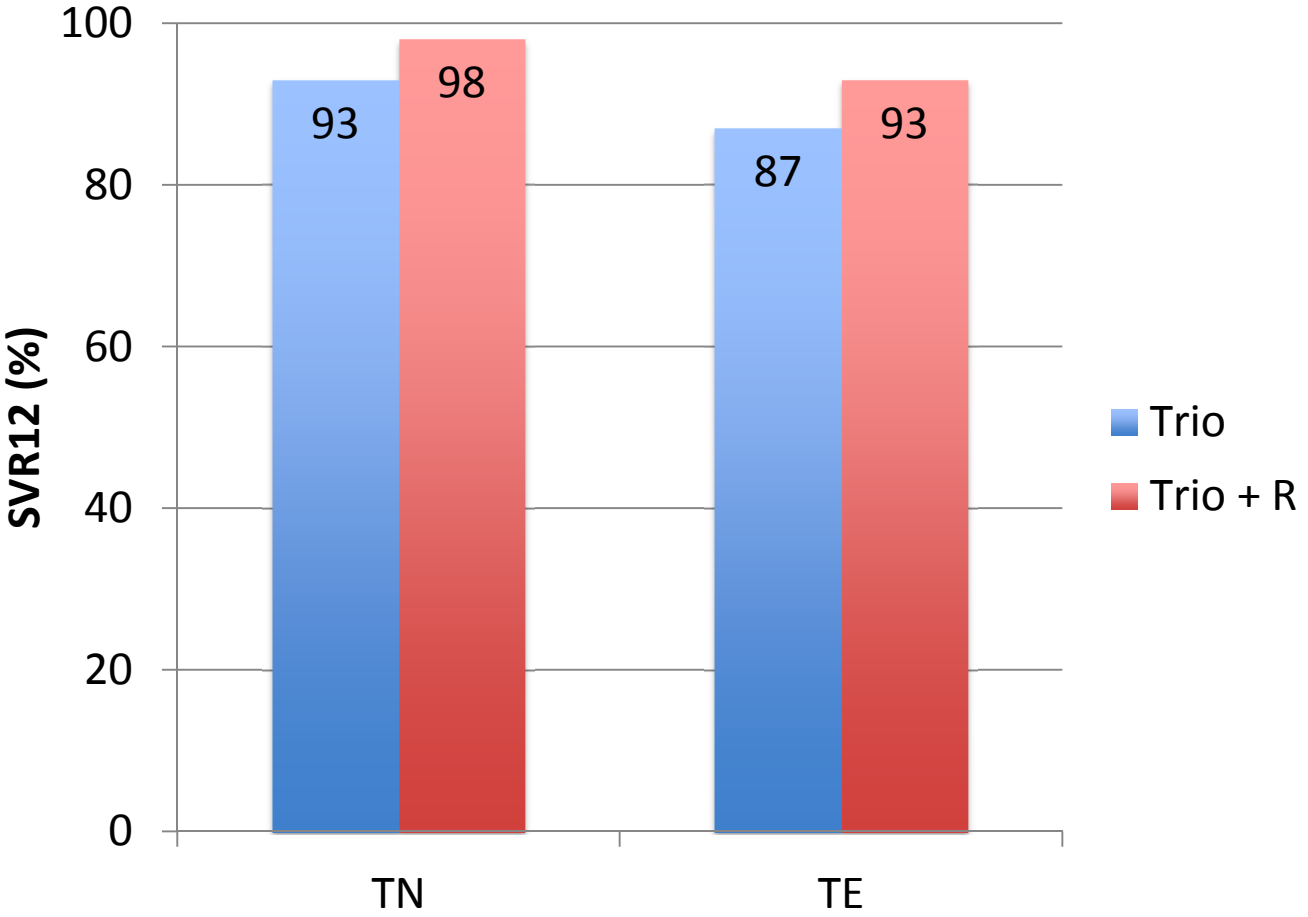
UNITY-2: BMS Trio Regimen

- Phase 3 study in naïve (n=112) and experienced (n=90) cirrhotics
  - Trio FDC [DCV 30mg/ASV 200mg/BCV 75mg] BID
  - Compensated cirrhosis (CPT A)
    - Plt >50k (26% of pts with Plt <100k)
    - INR <1.7
    - ALB >3.5



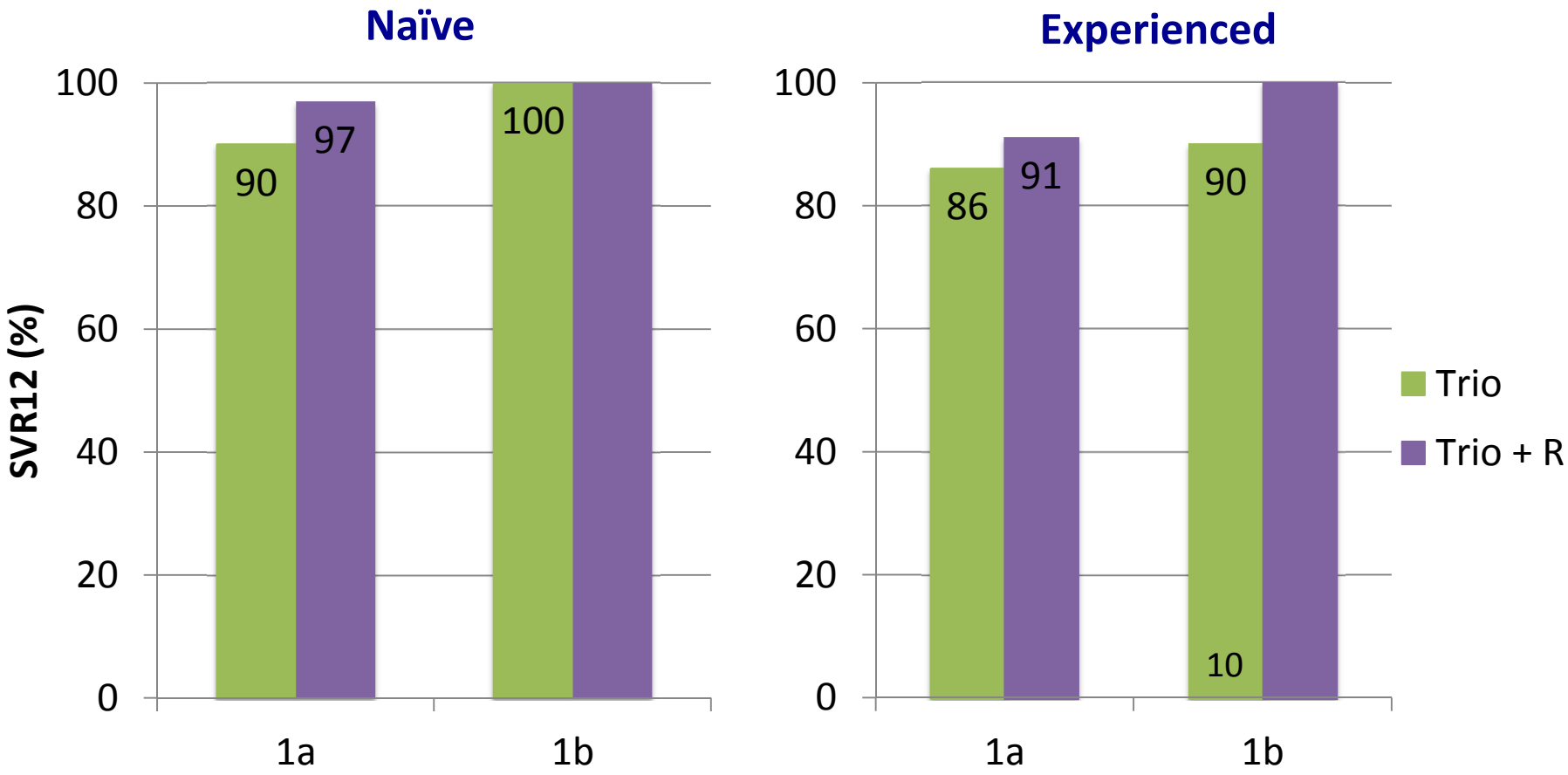
Muir A. #LB-2 AASLD 2014.

BMS Trio SVR12 Results



Muir A. #LB-2 AASLD 2014.

SVR12 by genotype



Muir A. #LB-2 AASLD 2014.

New regimen approvals for GT1

- BMS Trio
  - RBV for all 1a's
    - UNITY-1 (SVR12): 89% 1a vs. 98% 1b *Poordad F. AASLD 2014*
    - Do treatment experienced need 24 weeks?
      - Problem: not studied
  - Do TE 1b's need RBV?
- Grazoprevir/Elbasvir
  - Non-cirrhotic: 12 weeks no RBV
  - Cirrhotics: phase 3 will determine 12 vs. 16 weeks and role of RBV.

What is a truly pan-genotypic regimen?

- High efficacy across all genoytpes *with*
  - The same treatment duration
  - No need for RBV for some genotypes
- Contenders: most are nucleotide + NS5A
  - SOF/GS-5816
  - SOF/DCV
  - Grazoprevir/Elbasvir
  - The next wave
    - ACH-3102/3422 or ABT-493/ABT-530

Not all NS5A inhibitors are created equal

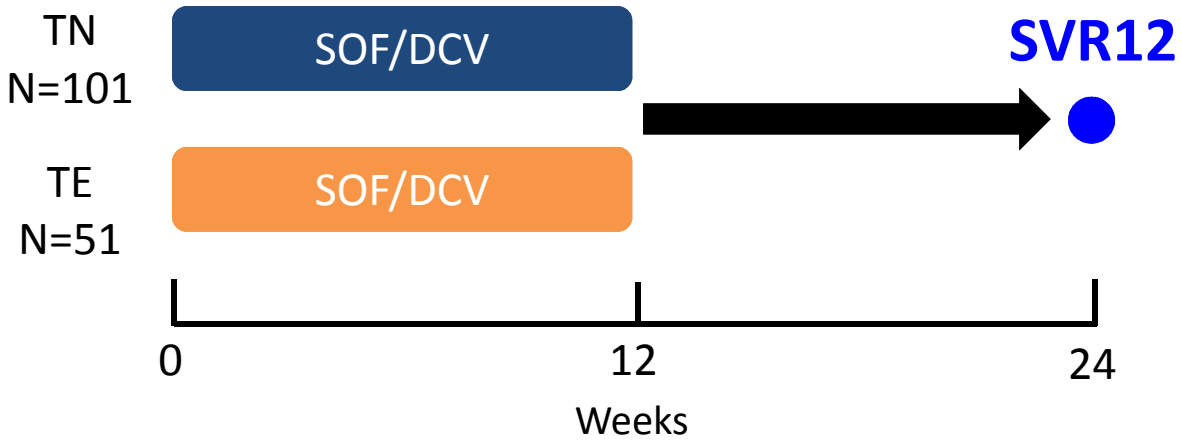
EC50 (pM)	1a	2a	3	4	6
LDV	34	21000	35000	110	120
DCV	50	71	150	12	--
GS-5816	12	9	12	9	6
Elbasvir	4	3	20	3	--
ACH-3102	26	<10x FC in EC50			
ABT-530	2	2	2	2	3

Later generation compounds retain activity against variants at polymorphic site (Q30, L31) and those associated with resistance (28, 30, 31, 58, and 93).

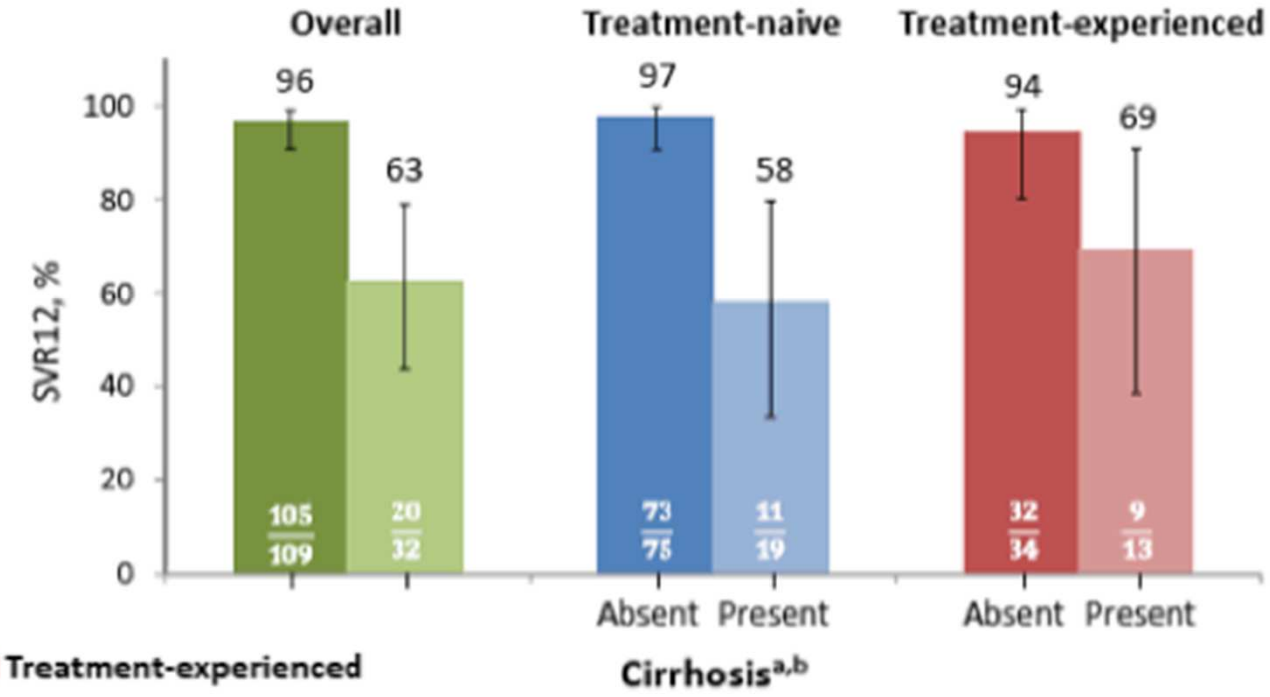
Wang C. AAC 2012. Zhao Y. #A845 EASL 2012. Ng T. #639 CROI 2014.

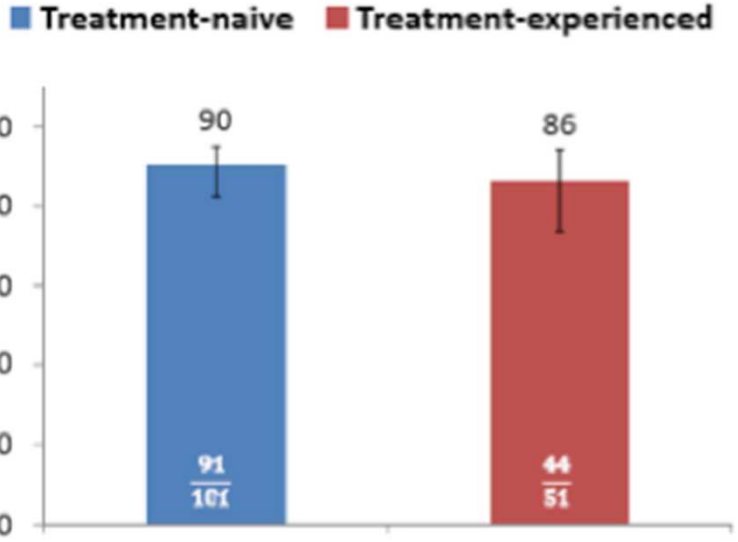
ALLY 3

- Phase 3 study of SOF/DCV in GT-3 subjects
  - Patients with cirrhosis included



Nelson DR. # AASLD 2014.

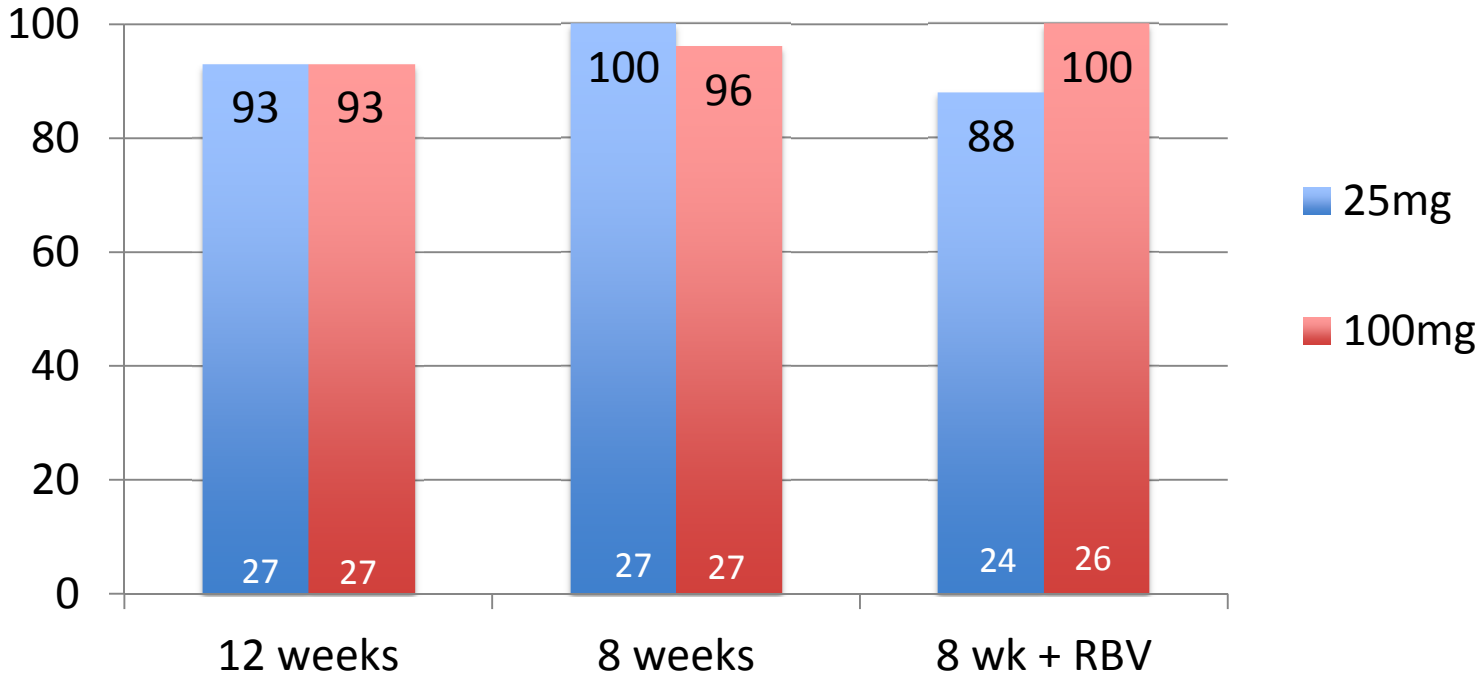




4% (11/32) had baseline platelet counts < 100,000/mm³

SOF + GS-5816 for GT3

- Treatment naïve, non-cirrhotic GT3
  - SOF + GS-5816 (25 or 100mg)
    - US Study: 12 weeks, no RBV
    - ELECTRON 2: 8 weeks +/- RBV



Everson G. EASL 2014. Gane E. # 79 AASLD 2014.

Great, but…

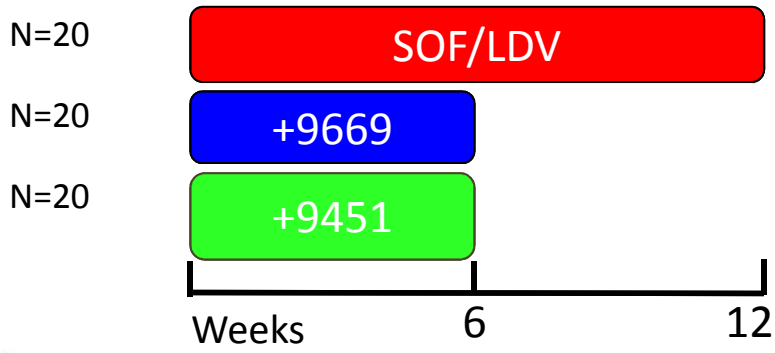
- We need data in tougher to treat populations
  - Treatment experienced
  - Cirrhosis
- ALLY-3: Sofosbuvr + Daclatasvir for 12 weeks
  - Only 63% SVR in GT3 cirrhotic patients
- Studies are ongoing
  - SOF/GS-5816: GT1, 4-6; GT2; GT3
  - ABT-493/530 in GT2/3
  - SOF/GZP/ELB in GT3

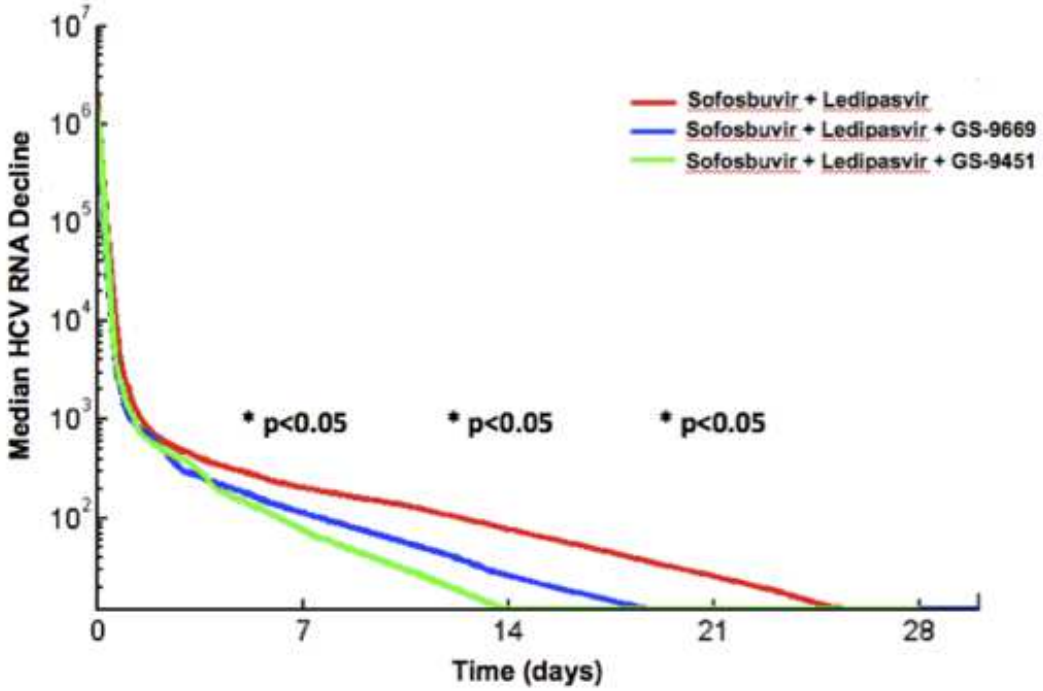
Nelson DR. #LB-3 AASLD 2014.

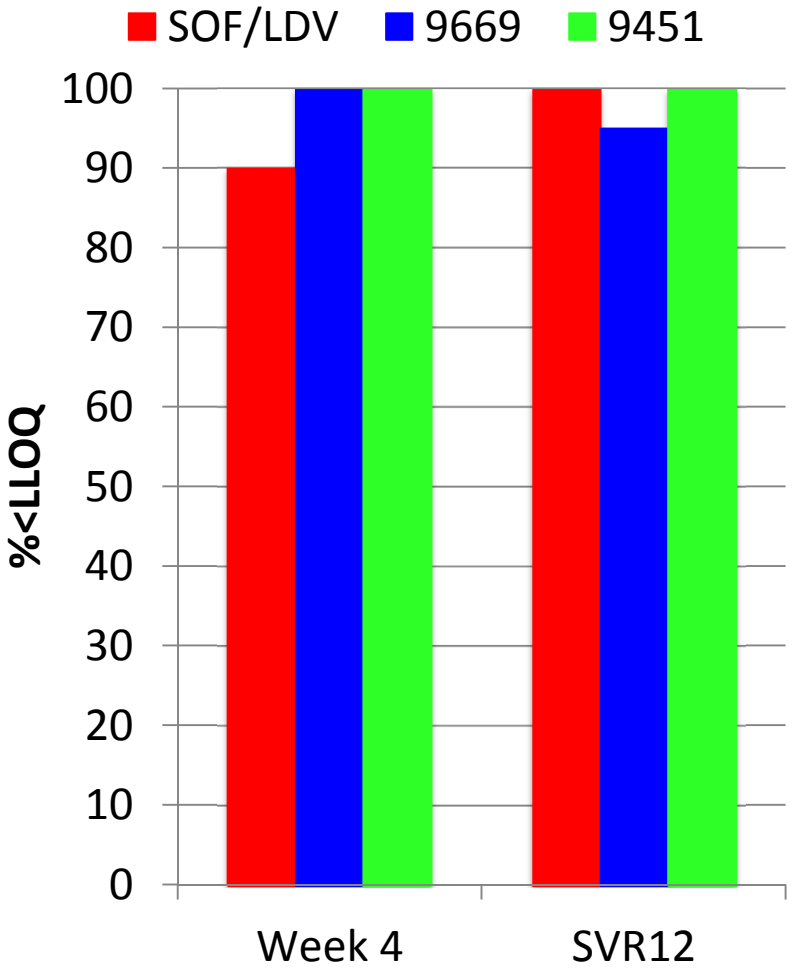
The race to shorten therapy.

- How much does it matter?
- How short can you go…and where are the diminishing returns?
  - Is it worth it if you have a lot of caveats?
    - Fibrosis stage
    - Genotype
    - Viral load
    - Co-infection
    - Etc, etc.

SYNERGY – the study that started it all



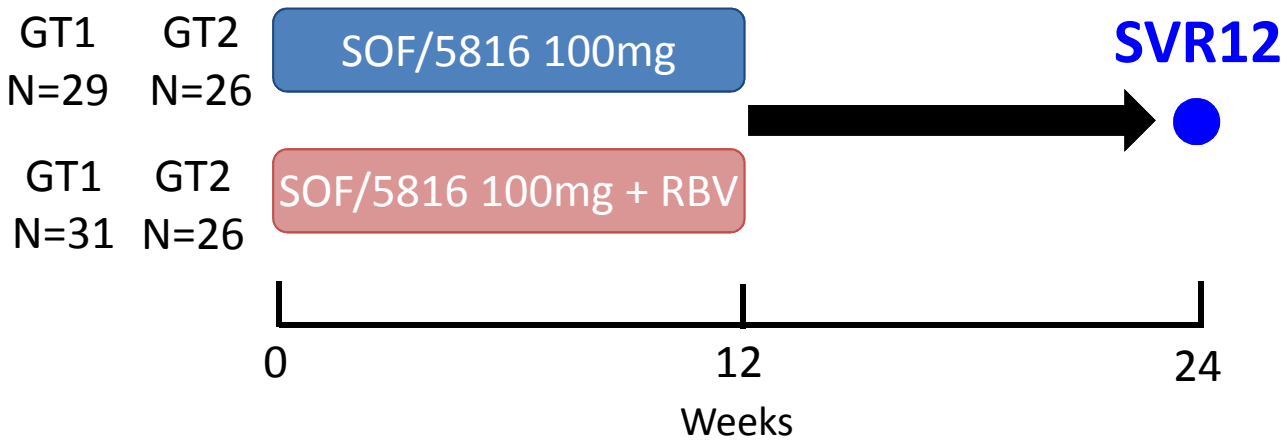




Kohil A. CROI 2014

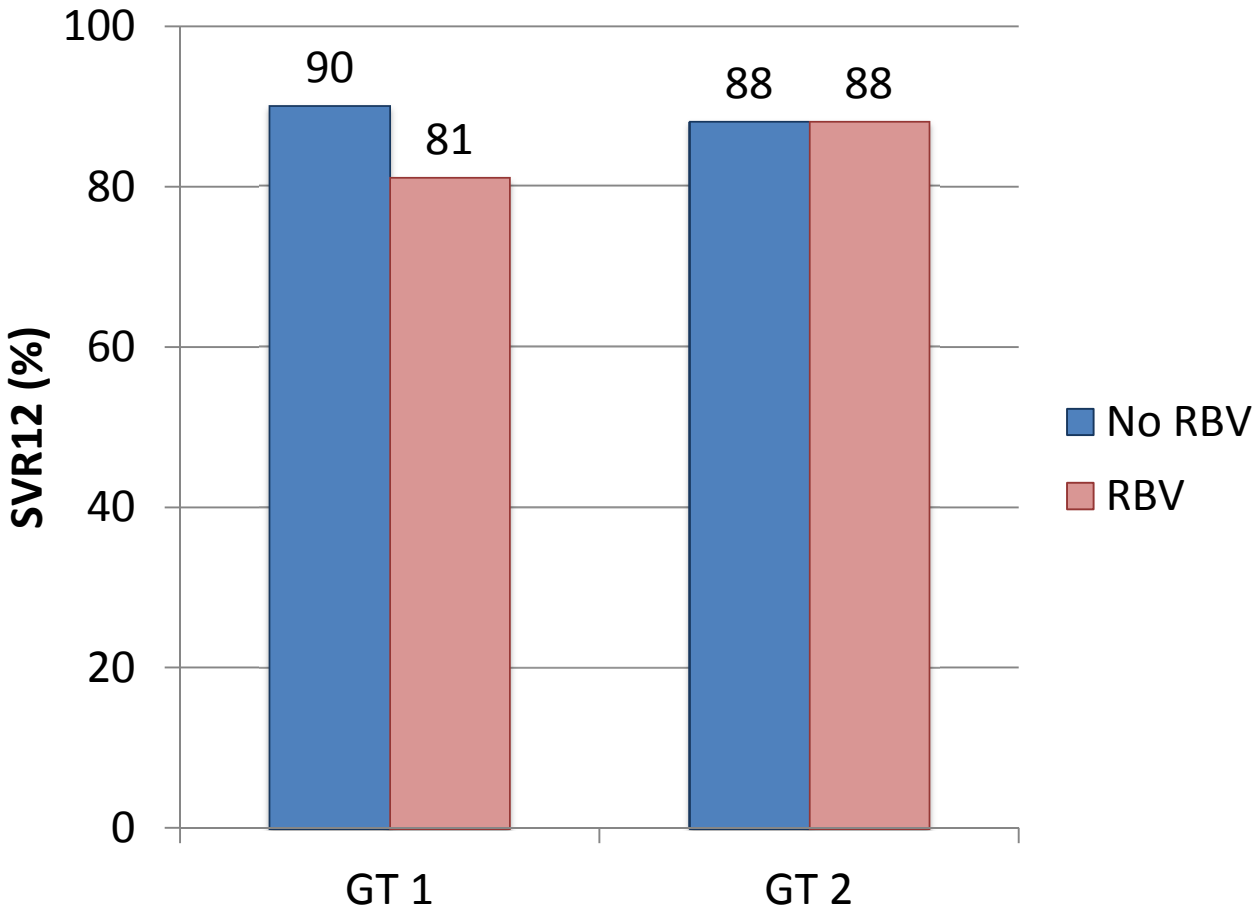
SOF/GS-5816 for 8 weeks

- Treatment naïve, non-cirrhotic patients



Tran T. #80 AASLD 2014.

SOF/GS-5816 for 8 weeks

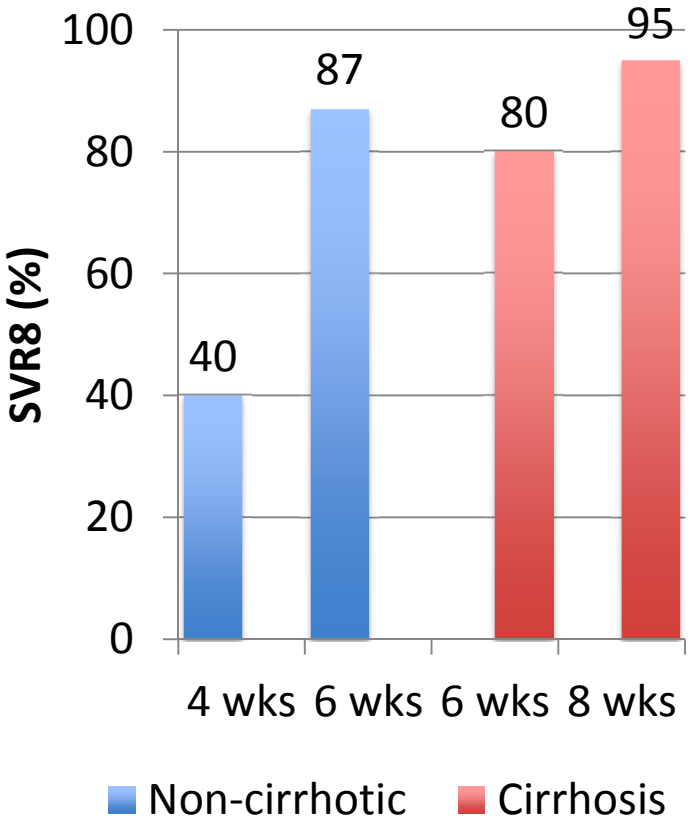


14/15 viral failures due to relapse.

Tran T. #80 AASLD 2014.

C-SWIFT Study

- Triple combination of SOF + GZP/ELB
  - Naïve, GT 1 subjects
    - Non-cirrhotic: 4 or 6 weeks
    - Cirrhosis: 6 or 8 weeks
  - 28/102 (27%) with relapse
    - 30% relapse in 1a
    - 17% relapse in 1b



Lawitz E. #LB-33 AASLD 2014.

Summary

- We are not there yet with DAAs in phase 3 for a truly pan-genotypic regimen
  - Particularly for tough to treat populations
    - GT3 cirrhosis
- Shortening therapy is nice…but should not be priority
  - Below 8 weeks significant drop off occurs
    - Subgroups become more important again!
    - There is a physiologic limit
  - Cost benefits are lost

NS5A RESISTANCE: CLINICAL SIGNIFICANCE?

NS5A resistance background

Genotype 1

- Similar resistance pattern for 1st gen NS5A
  - 1a: Q30E/K/R, L31M/V, Y93H/C 1b: L31M/V + Y93H
- ~15% with baseline RAVs
  - 1a: Q30R/H 1b: L31M/V, Y93H
- Selected RAVs are relatively fit and persist
  - 86% (63/73 1a) and 95% (56/59 1b) by population

Reddy KR. #1965 AASLD 2014.

Impact of NS5A baseline resistance is contextual

- IFN vs IFN-free
- Strength of surrounding DAAs

Impact of Baseline LDV RAVs on Treatment Outcomes

Study	+ IFN	SVR24 (%)	
		LDV RAV	Overall
248-0120 (TN)	No	8	48–58.5
248-0121 (TN)	Yes	50	80.5
256-0124 (TE)	Yes	37.5	69
256-0148 (TN)	Yes	76	60–83

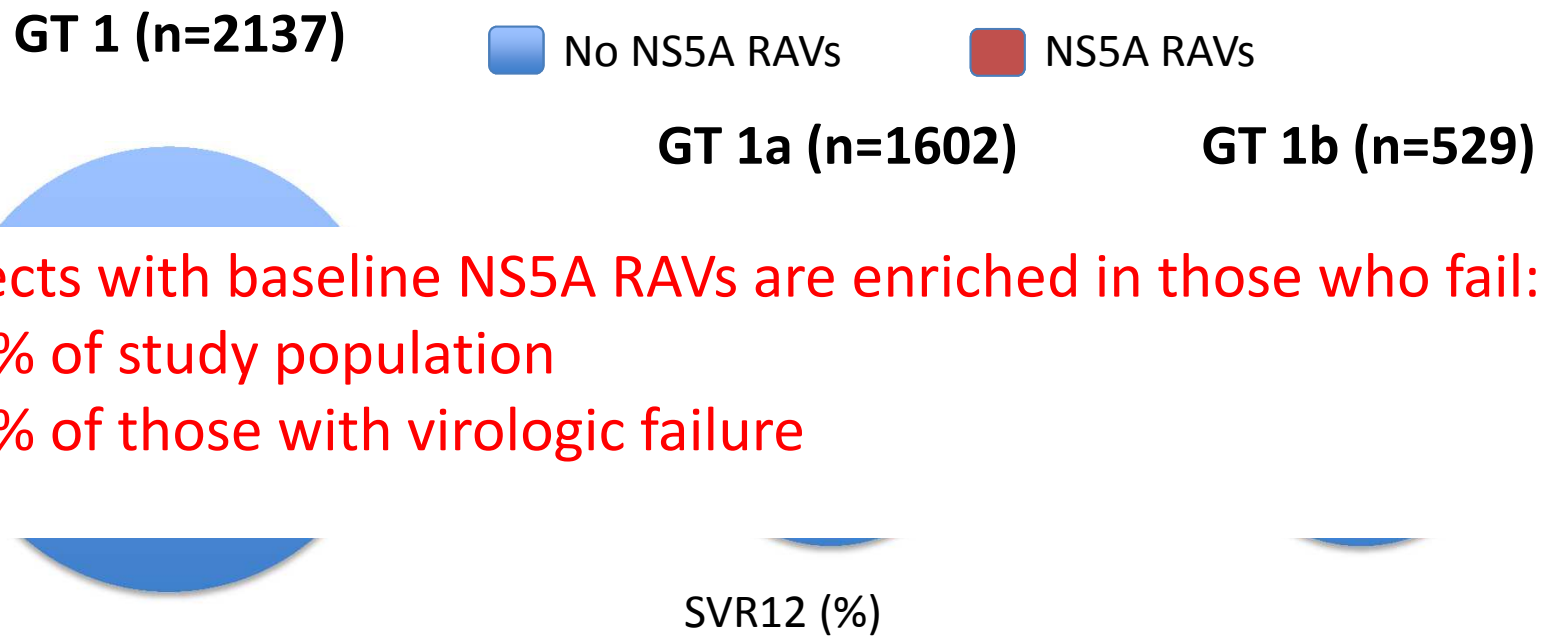
SVR24, sustained virologic response 24 wk after treatment end; TE, treatment experienced; TN, treatment naive.

38% SVR12 in ASV/DCV with baseline NS5A RAVs (compared to 85% overall)

Kitrinos KM. #1949 AASLD 2014. Manns M. EASL 2014

Baseline NS5A resistance and SOF/LDV

- Deep sequencing analysis of baseline samples (n=1904) in phase 2/3 SOF/LDV studies
  - ELECTRON, LONESTAR and ION studies

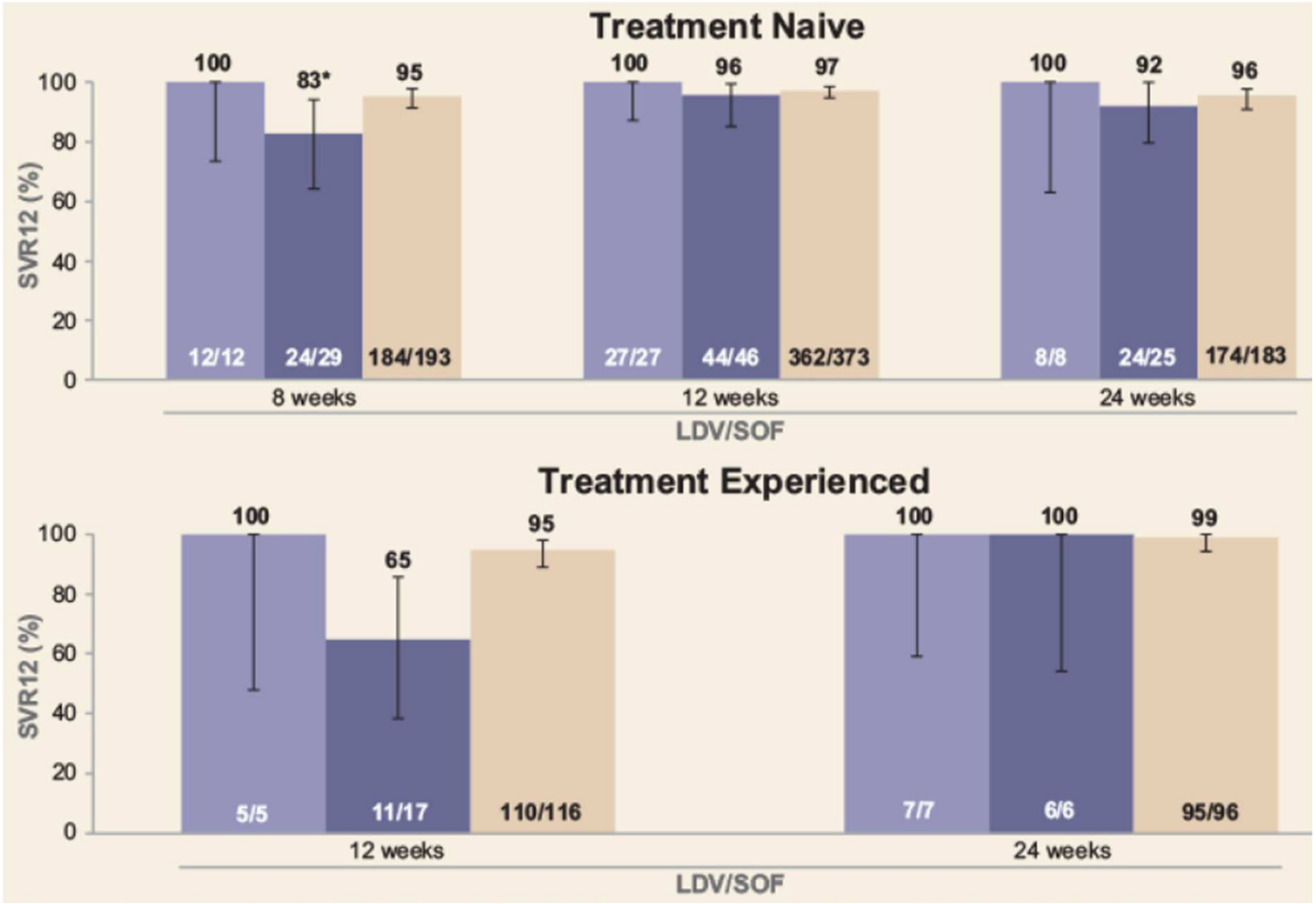


Subjects with baseline NS5A RAVs are enriched in those who fail:

- 16% of study population
- 43% of those with virologic failure

Sarrazin C. #1926 AASLD 2014.

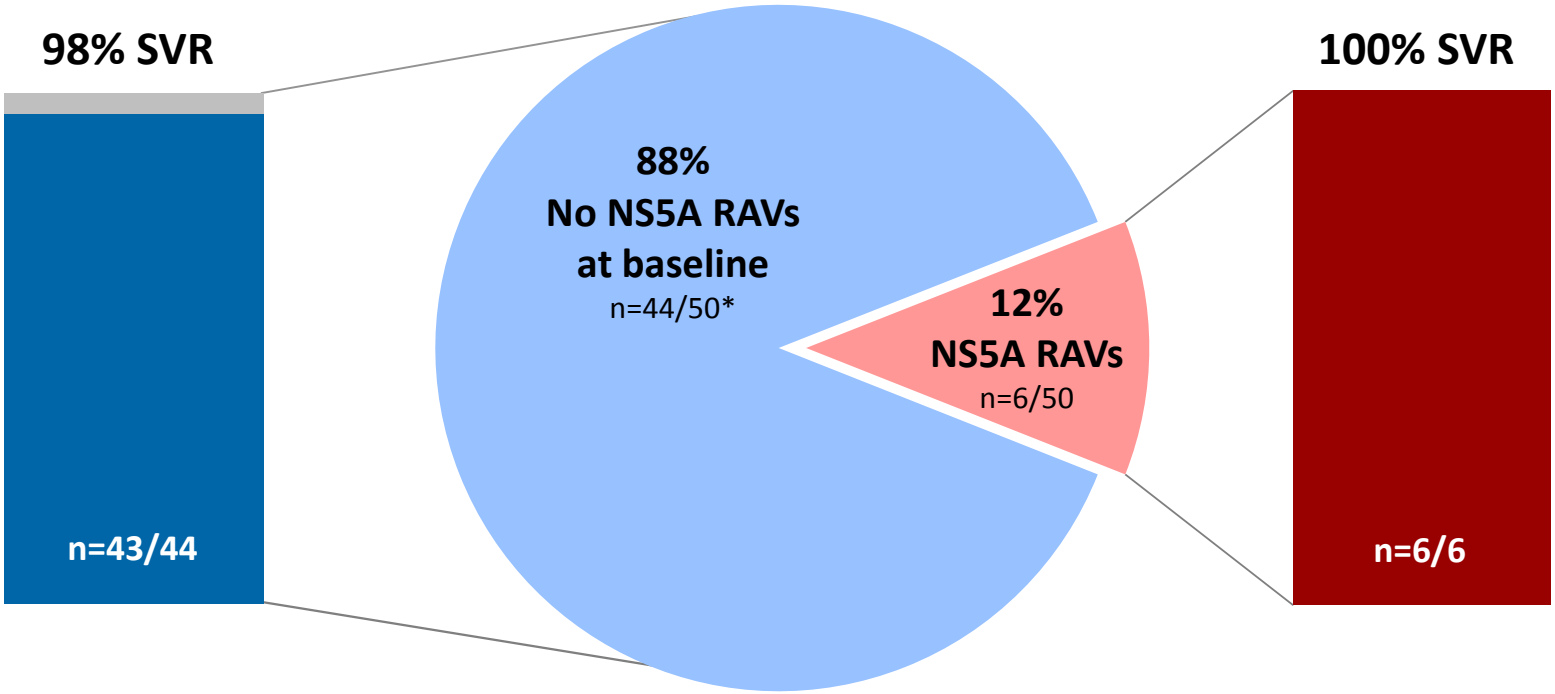
Baseline NS5A resistance and SOF/LDV



Sarrazin C. #1926 AASLD 2014.

Impact of baseline NS5A RAVs on outcomes in retreatment

- No patients had SOF-associated variant, S282T, detected at baseline
  - 2 patients had NS5B treatment-emergent variant L159F at baseline and achieved SVR



*1 patient's baseline results were not available.

Wyles D. #235 AASLD 2014

Conclusions

- The next 18 months wont be as exciting
  - Additional GT 1 regimens added:
    - BMS Trio
    - Grazoprevir/elbasvir
    - SOF/GS-5816
  - GT2/3
    - We will have IFN-free regimens without RBV
    - 12 weeks for GT3
      - Except cirrhosis?
      - Data on 24 wks?
  - 8 weeks with current investigational agents is about as short as we can go
  - NS5A resistance likely impacts response
    - Is the effect large enough to warrant baseline testing?


Thank You!
My work is done.