Interferon-free DAA Therapy: Where to from here?

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Disclosures

- Research: Abbvie, Abbott Gilead, Janssen, Merck, Wako Diagnostics
- Consulting: Abbvie, Contravir, Gilead, Merck,

Outline

- Where we are: Current state of therapy
- The future: Where we are going
  - Shorter therapy
    - Do we need shorter therapy?
    - Can we predict the minimum duration?
  - Are there other ways to simplify further?

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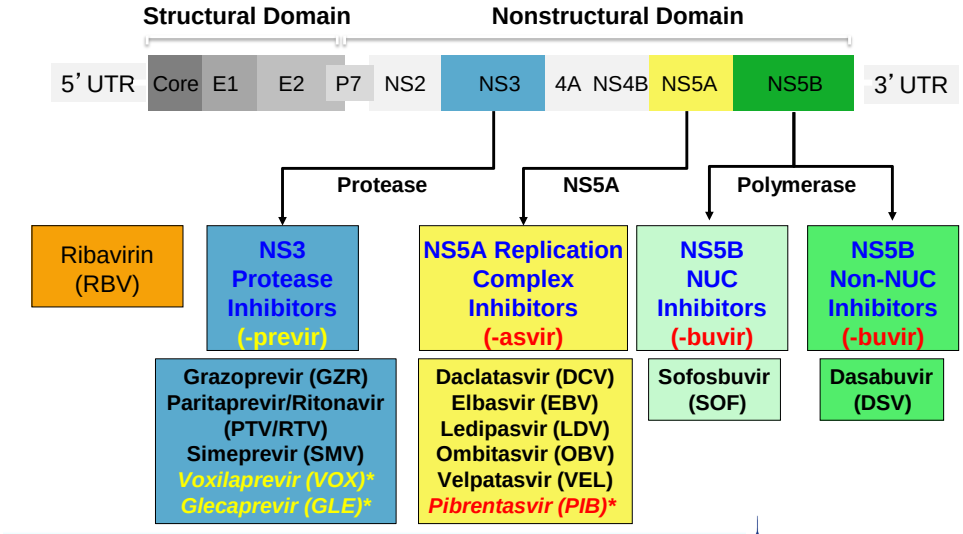
Great options available



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Great options across the board

HCV GT	Recommended Regimens	
	SOF Based	PI Based
GT1	▪ SOF/LDV ▪ SOF + SMV ▪ SOF/VEL ▪ SOF + DCV	▪ GZR/EBV ▪ PTV/RTV/OBV + DSV + RBV (no RBV G1b) ▪ **GLE/PIB**
GT2	▪ SOF/VEL	▪ **GLE/PIB**
GT3	▪ SOF + DCV ▪ SOF/VEL	▪ **GLE/PIB**
GT4	▪ SOF/VEL ▪ SOF/LDV	▪ PTV/RTV/OBV + RBV ▪ GZR/EBV ▪ **GLE/PIB**
GT5/6	▪ SOF/VEL ▪ SOF/LDV	▪ **GLE/PIB**

- All deliver SVR rates >95%
- 8-12 weeks, 1-3 tabs/day
- All safe & well tolerated
- ***You can't go very wrong… (but you can go a bit wrong and there's value in getting it right the first time – details matter → look them up!)***

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What's new?
Can treatment get any easier?

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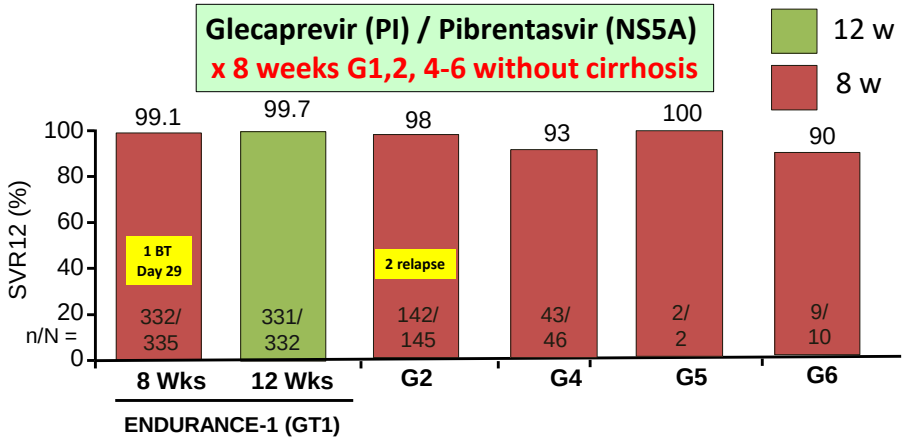
An 8 week option beyond G1



- Highly effective 3 pills per day x 8 weeks G1, 2, 4–6 without cirrhosis
- Equally effective naïve or experienced (PR +/- SOF)

Zeuzem S, et al. AASLD 2016. Abstract 253
Hassanein TI, et al. AASLD 2016. Abstract LB-15.

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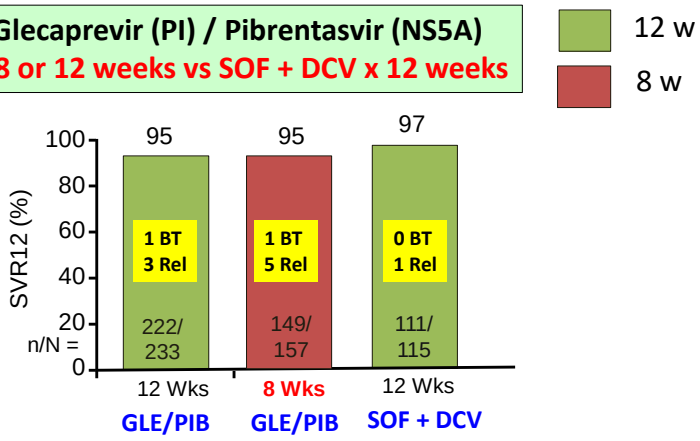
What about G3 infection?

Glecaprevir (PI) / Pibrentasvir (NS5A)
x 8 or 12 weeks vs SOF + DCV x 12 weeks



Effective for 8 weeks in ***naïve*** **G3** ***without*** **cirrhosis**

Zeuzem S, et al. AASLD 2016. Abstract 253
Hassanein TI, et al. AASLD 2016. Abstract LB-15.

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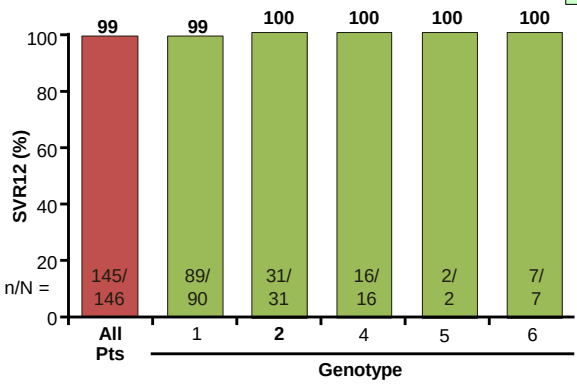
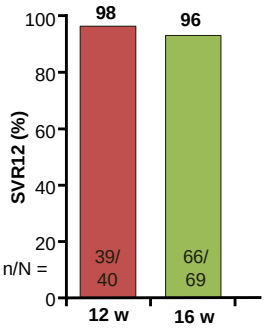
Who needs longer therapy?

Glecaprevir (PI) / Pibrentasvir (NS5A) X 12 w
G1,2, 4-6 with compensated cirrhosis



Glecaprevir /Pibrentasvir for G3
12 w naïve + comp cirrhosis,
16 w PR/SOF +/- cirrhosis



Cirrhosis all GT and G3 experienced – extend therapy

Forns EASL 2017
Wyles AASLD 2016

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Summary GLE/PIB

- Highly effective pan-genotypic regimen
  - **8 weeks** – G1, 2, 4-6 no cirrhosis
    G3 **naïve** no cirrhosis
  - **12 weeks** - G1, 2, 4-6 with compensated cirrhosis
  - **16 weeks** – G3 experienced +/- compensated cirrhosis
- Hepatically cleared – **safe in severe CKD/dialysis**
- Well tolerated - no major AE signal
- Contains a protease inhibitor
  - **Contraindicated in decompensated cirrhosis**
  - Fewer drug interactions than earlier PIs

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Options for patients who fail first-line therapy…

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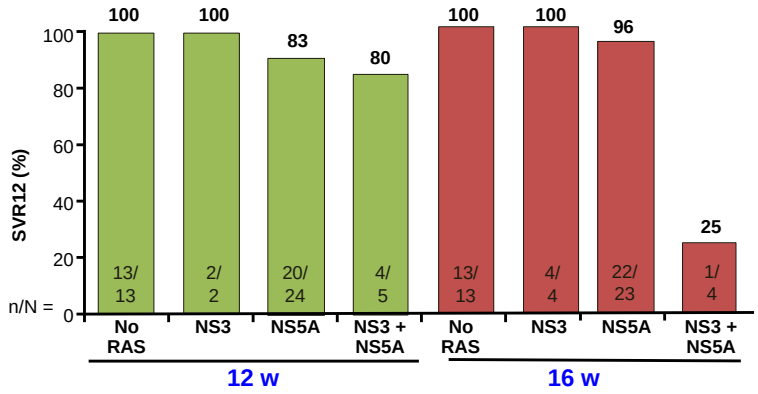
What about GLE/PIB?

GLE/PIB x 12 or 16 w PI +/- NS5A failures, 30% cirrhosis



- Particularly if limited to G1a (where it matters), NS5A had a big effect
- Resistance testing required – probably not the first choice currently

Poordad EASL 2017

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What about SOF/VEL/VOX – adding in a protease inhibitor?

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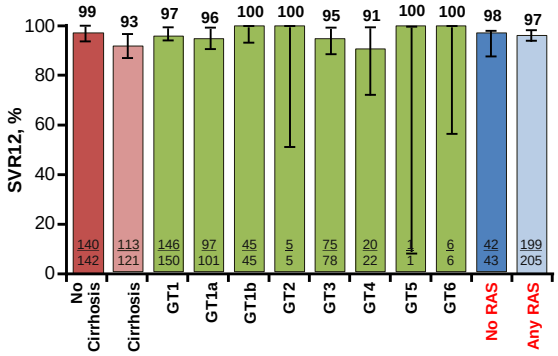
POLARIS 1 - Prior NS5A Failures

SOF/VEL + **PI VOX (GS-9857)** x 12 weeks → G1-6 prior NS5A, 41% cirrhosis



- 7 virologic failures
  - 6 relapse
  - 1 breakthrough
- All cirrhotic
  - **G3 (n=4), G1a (n=2), G4 (n=1)**
- 6M, 1F
- Only notable **VOX AE is mild diarrhea**

- Remarkably few failures – very promising salvage option
- Baseline resistance apparently not predictive of failure

Bourliere NEJM 2017

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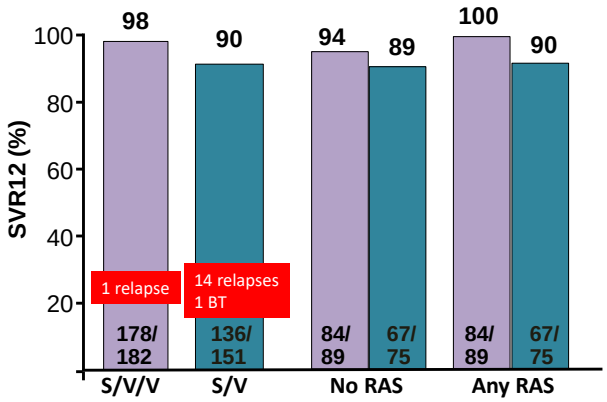
POLARIS 4 - Prior non-NS5A failures

SOF/VEL/**VOX** vs SOF/VEL x 12 weeks → G1-4 prior **non-NS5A DAA**, 46% cirrhosis



- **Virologic Failures**
  - **S/V/V n=1 (G1a)**
  - **S/V n=15**
    - **G1a – n=5**
    - **G3 – n=8**
    - **G1b – n=1**
    - **G2 – n=1 BT**
  - **12M/3F**
  - **9 cirrhotic**

- Surprisingly triple therapy more effective…intrinsically 'harder to cure'
- **G1a/3 – SOF/VEL/VOX** **Other Genotypes – SOF/VEL alone**

Bourliere NEJM 2017

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Summary of where are we now

- Remarkably effective & simple therapy
  - 8 weeks for non-cirrhotics - all genotypes
  - 12 weeks for cirrhotics – all genotypes
  - Effective retreatment strategies with limited need for resistance testing (maybe G1a & G3)
  - Equally effective in key sub-groups – PWID, CKD

Outline

- Where we are: Current state of therapy
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  - **Shorter therapy**
    - **Do we need shorter therapy?**
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Pros & Cons of shortening

The benefits are less obvious than one might assume

- **Eas… atients**
  - Reduc…
  - Increased a…
  - Simplicity
  - Preference
- **Easier for treaters**
  - Capacity
  - Monitoring
- **Cheaper**
  - Fewer doses = fewer $

Cons (or at least non-pros)

- **Therapies are easy & safe**
  - Overtreatment is safe
  - Toxicity could increase…
  - Adherence may not change
  - Could increase complexity…
- **…rapies are easy & safe**
  - …ed or even no monitoring
  - E… …act on capacity…
- **DAAs ar… …to produce**
  - New drugs … …ally increase costs…
- **Relapse**
  - Always a risk

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So should we aim for shorter therapy?

- All things being equal, yes
- But ‘all things being equal’ is a big question mark
- Assuming:
  - Similar or identical SVR rate
  - Similar or better safety profile
  - Similar complexity to treatment – ***simplicity may trump short***

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Where is short therapy most important?

- **Harder to reach populations**
  - Homeless
  - PWID
  - Incarcerated
- **Limited capacity or funding**
  - Low/middle income countries
  - Patients who 'self-pay' using cost-per-pill pricing
  - Rural/remote regions (?)

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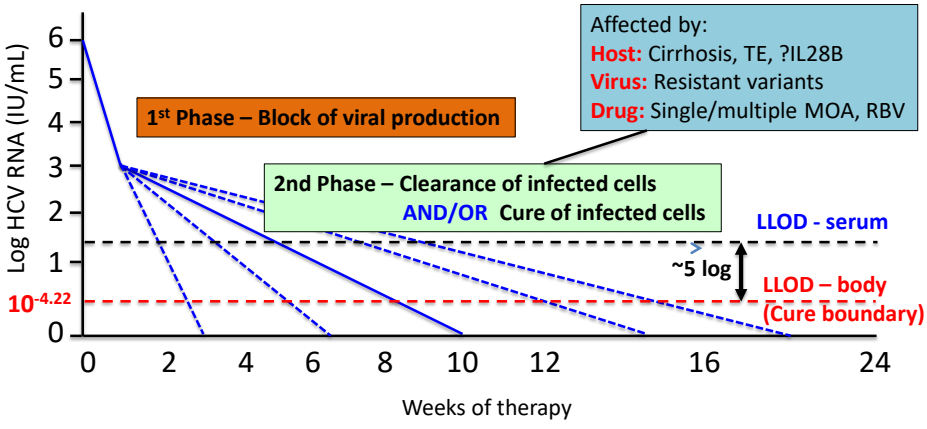
How long do we *need* to treat?



Perelson Nat Rev Gastro Hep 2015

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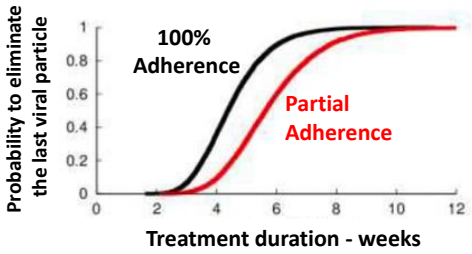
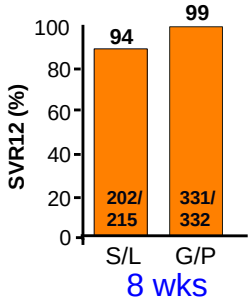
What does the model predict?

Theory – Telaprevir monotherapy



Clinical Trials: SOF/LDV or G/P



Assume: 100% adherence
No resistance – ie really for combo DAA

Model predicts fairly well → 95+% with 8 weeks of highly effective DAAs

Guedj Hepatology 2011, Kowdley NEJM 2014, Zeuzem AASLD 2016

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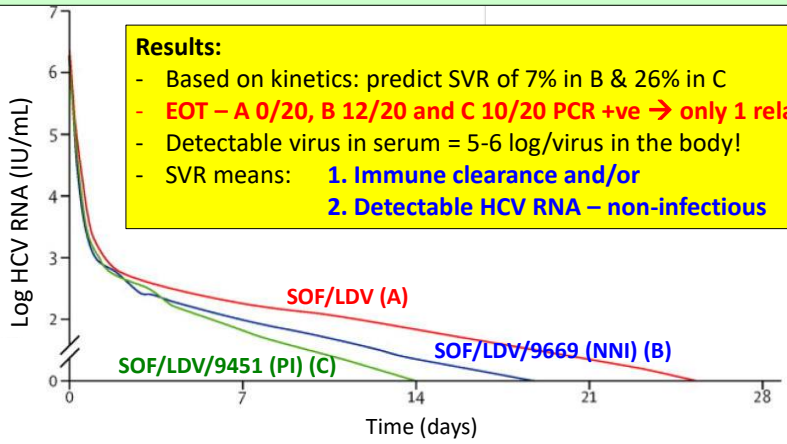
But it's never that simple…

SYNERGY: **SOF/LDV x 12w** vs **SOF/LDV/9660 (NNI)** or **SOF/LDV/9451 (PI) x 6w**



Results:
- Based on kinetics: predict SVR of 7% in B & 26% in C
- **EOT – A 0/20, B 12/20 and C 10/20 PCR +ve → only 1 relapse!**
- Detectable virus in serum = 5-6 log/virus in the body!
- SVR means: **1. Immune clearance and/or**
  2. Detectable HCV RNA – non-infectious

Kohli Lancet 2015

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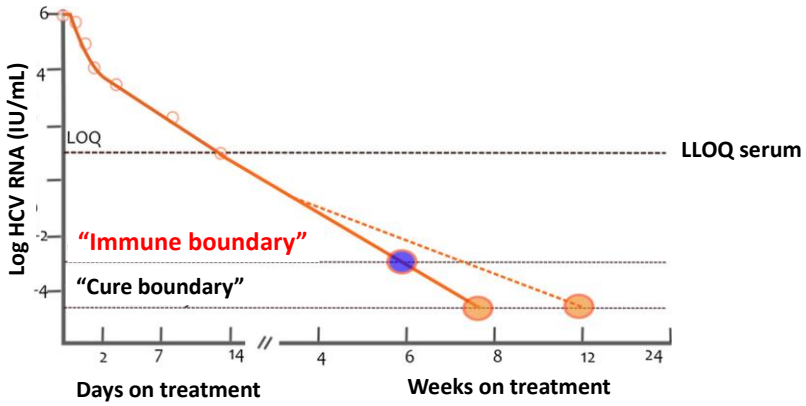
Not as simple as the slope…



- 'Throws off predictions' – poor understanding/prediction of immune boundary
- Means kinetics alone are probably not enough to predict

Perelson Nat Rev Gastro Hep 2015

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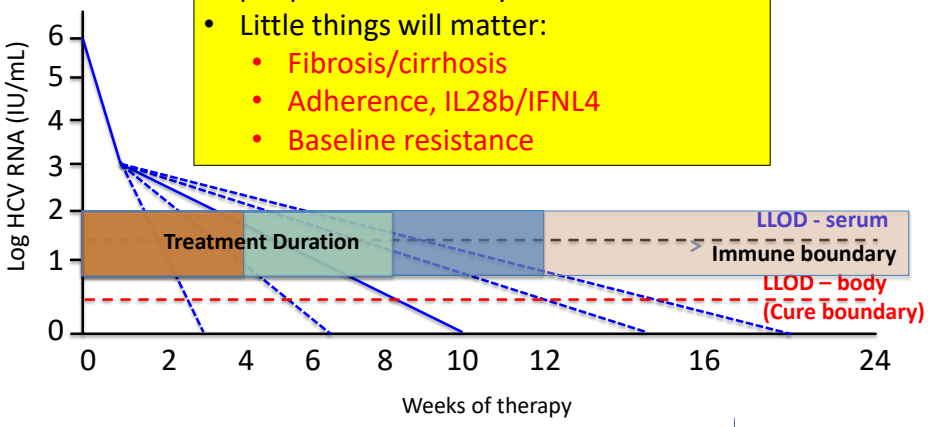
Over-treatment of most patients

- Shorter durations will still cure some people but not everyone
- Little things will matter:
  - Fibrosis/cirrhosis
  - Adherence, IL28b/IFNL4
  - Baseline resistance



Perelson Nat Rev Gastro Hep 2015

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Success rates of 95+% in trials and the real world mean…

- We are almost certainly over-treating most people
- We're not that good!
  - ***To get such excellent results, most people do not NEED 12 (or even 8) weeks***
- Significant variability in viral kinetics
- We are treating to the cure the 'slow' responders (and curing the 'fast' responders in the process)

So if 12 weeks is 'over-treatment', how short can we go?

Approaches to shorten

- DAAs alone
- DAAs in selected populations
  - Baseline
  - On-treatment response
- New approaches

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- **DAAs alone**
- DAAs in selected populations
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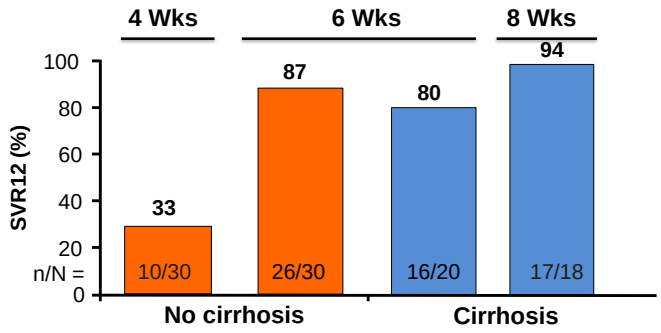
How short can we go?

Grazoprevir (PI) + Elbasvir (NS5A) + Sofosbuvir (Nuc) x 4 – 8 weeks in G1 with or without cirrhosis



- Very potent regimen → 4 weeks clearly inadequate

Gane EASL 2015

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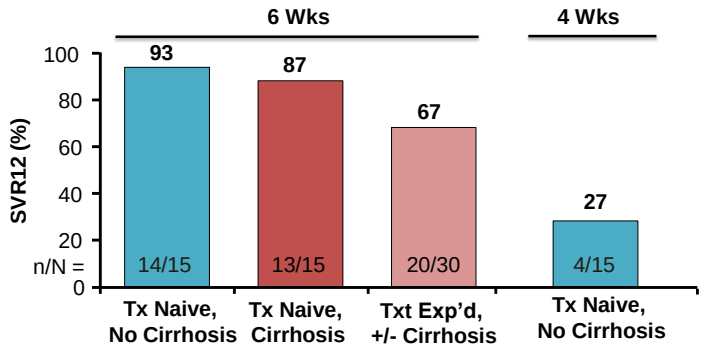
6 weeks seems to be the edge of the cliff for DAAs…

SOF/VEL (NS5A) /VOX (PI) x 4 or 6 weeks



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Gane EASL 2015

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Approaches

- DAAs alone
- **DAAs in selected populations**
  - **Baseline**
  - **On-treatment response**
- New approaches

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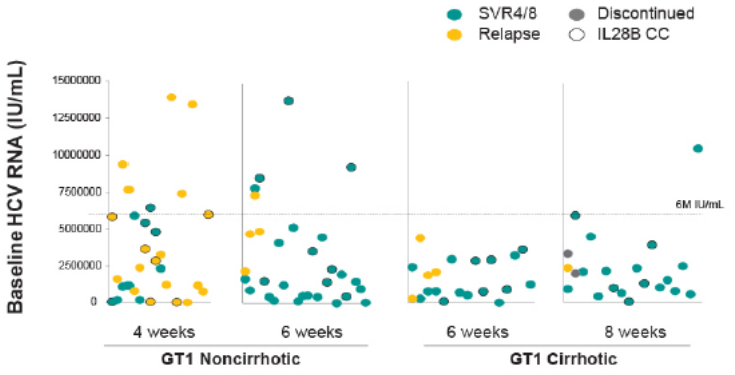
Can we predict who needs only 4 weeks?



- High baseline viral load predicts failure
- But low baseline viral load nor IL28B CC predict success…

Lawitz AALSD 2014 LB

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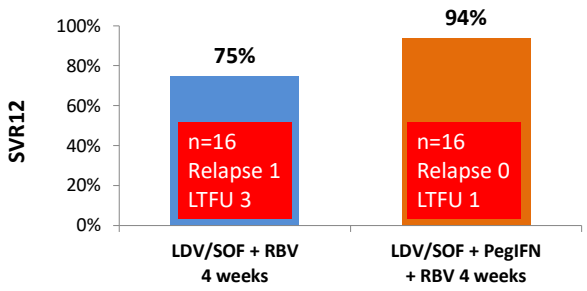
Choosing the right population: A very provocative trial!

PWID – **4 weeks** of SOF/LDV + RBV +/- Peg
G1 or 3 (and 1 G2), TN, on OST, F0-2



- Single centre study but interesting…
- ? Partial immunity from repeated exposures?

Overhuis AASLD 2016 Abstract 921

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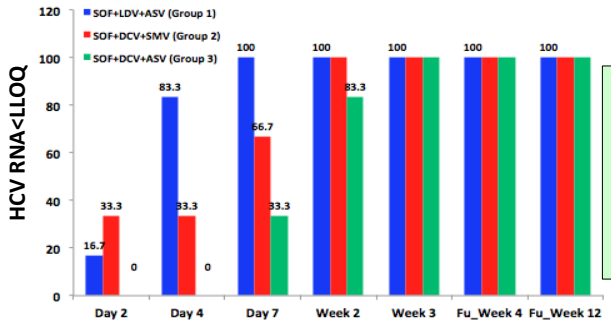
Back to response-guided therapy?

SOF + NS5A + PI → **if HCV RNA<500 at D2 → 3 weeks total therapy**, if not 8-12 weeks SOF/LDV



Outcome:
- 18 of 26<500 IU by d2
- 100% SVR with 3 wks of tx
- Others SVR with 12w of SOF/LDV
- **Overall 69% 3 weeks of therapy and 100% SVR**

- Critical factors: **G1b, Asian, IL28B CC**
- Weigh 'complexity' vs 'shorter therapy' → cost saving for patients buying their own medications (China)

Lau Lancet Gastro-Hep 2016

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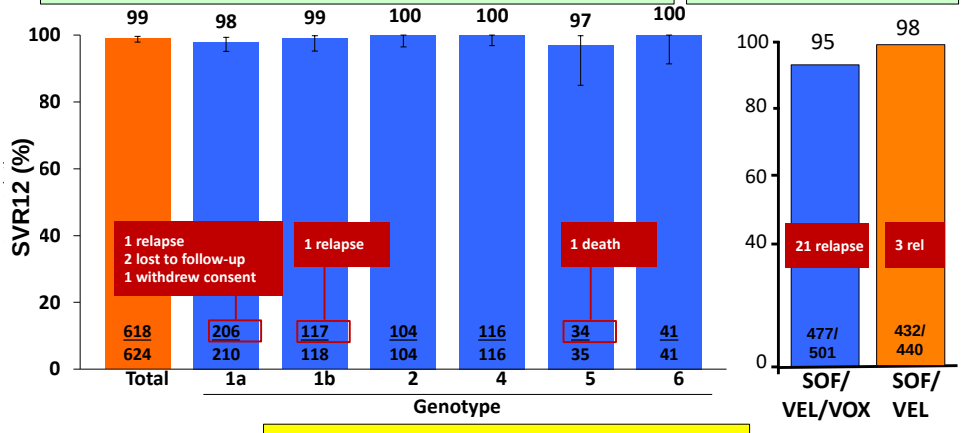
Alternative: Over-treat, but 1 size fits all

SOF + Velpatasvir (GS-5816) (NS5A) x 12 wks in
G1, 2, 4, 5, 6 – Naïve/Experienced +/- cirrhosis

SOF/VEL x 12
vs **SOF/VELVOX x 8**



Adding drugs to shorten…doesn't always work

Feld NEJM 2015, Jacobson Gastro 2017

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Other ways to simplify

SMART-C

Now:

- **Monitoring** – simplify! → SMART-C
  - **S**implified **M**onitoring – **A** **R**andomized **T**rial in Hepatitis **C**
    TN, non-cirrhotic, G1-6 → G/P x 8w → call at w4 & 8 but no visits vs SOC
- **Diagnostics**
  - Point-of-care rapid test with no genotyping

Future:

- **Depot formulation** – 1 injection = cure
- **DAA + host-targeting agent** (e.g. mir122 inhibitor)
- ***Is there an adequate 'market' for development???***

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Summary

- Current therapy is outstanding…likely as good as it's going to get!
- Shorter therapy is potentially attractive but ONLY if equally *safe, effective and simple*
- Cost alone should not be the primary reason to shorten – pricing should be per course of Tx
- Modeling predicts most will need 8 weeks or less
- To go below 8 weeks with DAAs alone – baseline or on-treatment response – not 'one size fits all' – is complexity worth the effort? ***In most scenarios, probably not…***
- To get to 4 weeks or shorter, will likely need more than DAAs

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Rational combinations

NUC + NS5A	SOF/LDV – G1/4 SOF/VEL – G1-6 SOF + DCV – G-6
PI + NS5A + Non-Nuc	PrOD +/- RBV – G1/4
PI + NS5A (2nd Generation)	EBV/GZV– G1/4 GLE/PIB – G1-6
Nuc + NS5A + PI	SOF/VEL/VOX – G1-6 (retreatment)

- All deliver SVR rates >95%
- 8-12 weeks, 1-3 tabs/day
- All safe & well tolerated
- ***You can't go very wrong…***
(but you can go a bit wrong and there's value in getting it right the first time – the details matter → look them up!)