NORTHWEST AIDS EDUCATION AND TRAINING CENTER

CROI 2014 – Hepatitis & Liver Abstracts

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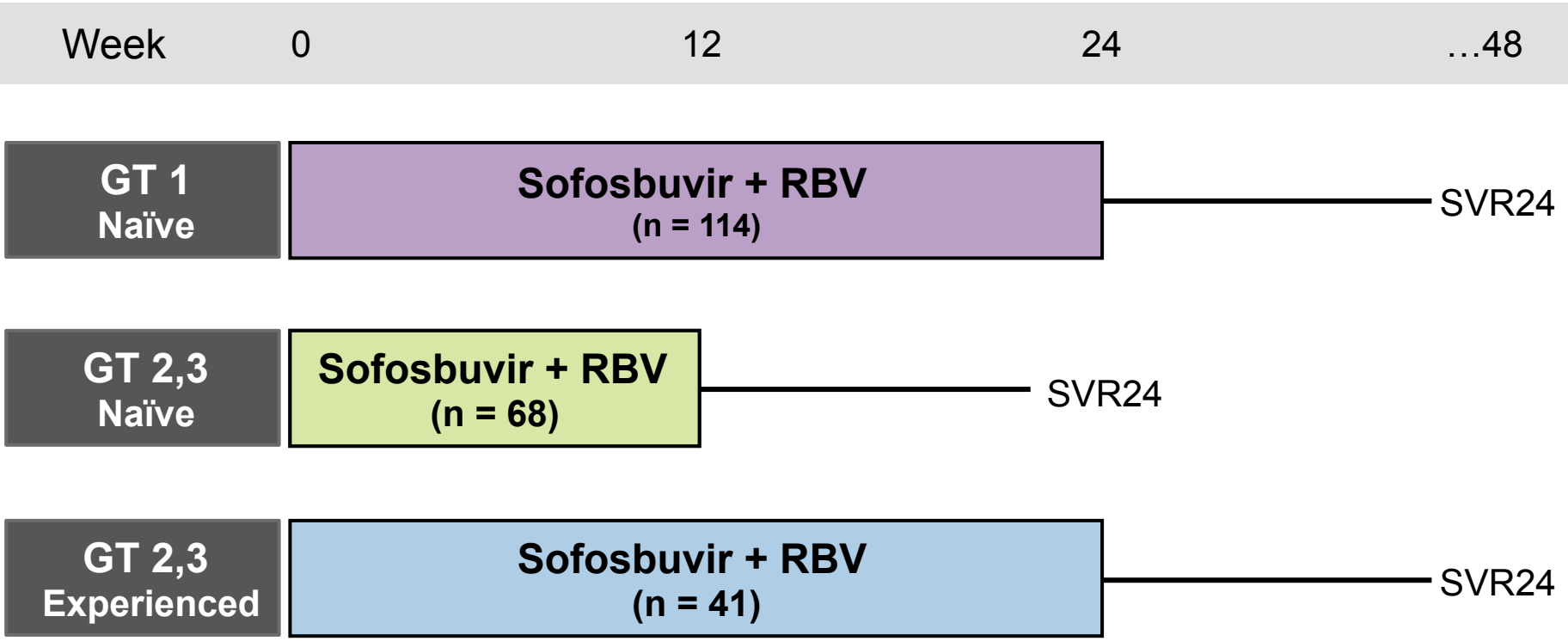
PHOTON-1 Study
Interferon-free HCV Therapy in HIV-infected Patients

- Sofosbuvir
  - NS5B nucleotide polymerase inhibitor (chain terminator)
  - Broad antiviral activity & clinical efficacy against GT 1-6
  - High genetic barrier to resistance
  - Once-daily oral 400-mg tablet
  - FDA approved in December 2013 for both mono-infected and co-infected HCV patients
  - Sofosbuvir + ribavirin dual therapy for 12-24 weeks can result in SVR 68-97% in monoinfected patients

Sofosbuvir and Ribavirin for HCV-HIV Coinfection
PHOTON-1 Trial: Study Design



Drug Dosing
Sofosbuvir: 400 mg once daily
Ribavirin (weight-based and divided bid): 1000 mg/day if < 75kg or 1200 mg/day if ≥ 75kg

Naggie S, et. al. CROI 2014. Abstract 26.

Sofosbuvir and Ribavirin for HCV-HIV Coinfection
PHOTON-1 Trial: Participants

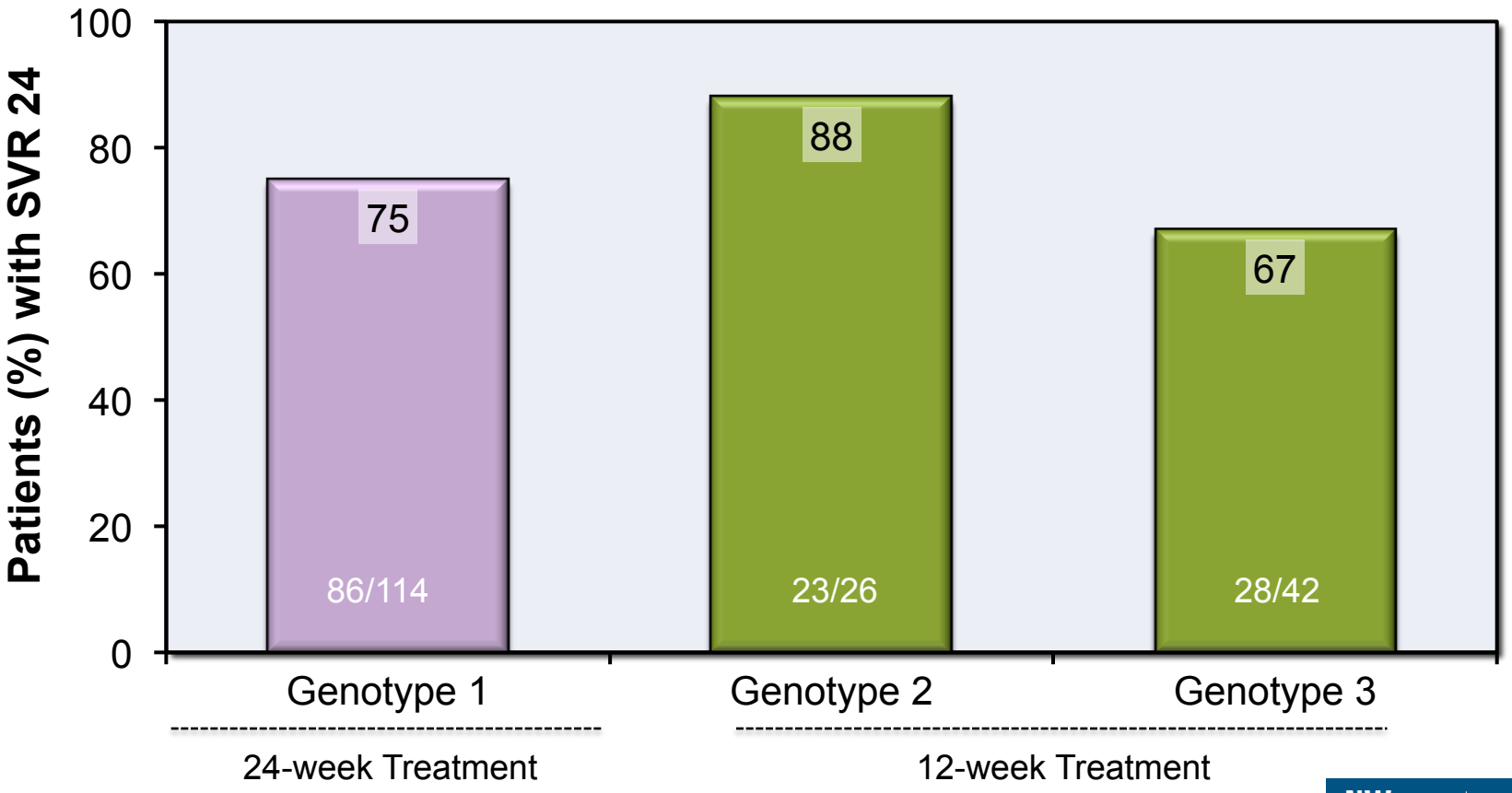
	Treatment Naive		Treatment Experienced
	GT 1 (n=114)	GT 2/3 (n=68)	GT 2/3 (n=41)
Age, mean (range)	48 (25-70)	49 (24-71)	54 (34-68)
Male, %	82%	81%	90%
Black, %	32%	12%	17%
IL28B CC genotype, %	27%	37%	49%
Cirrhosis, %	4%	10%	24%
On ART§, %	98%	90%	95%
CD4 count, cells/mm^3, mean	636	585	658

§TDF/FTC plus efavirenz, r-ATV, r-DRV, raltegravir, rilpivirine

Naggie S, et. al. CROI 2014. Abstract 26.

Sofosbuvir and Ribavirin for HCV-HIV Coinfection
PHOTON-1: Results for Treatment-Naïve Patients

PHOTON-1: SVR 24 HCV RNA <25 IU/ml



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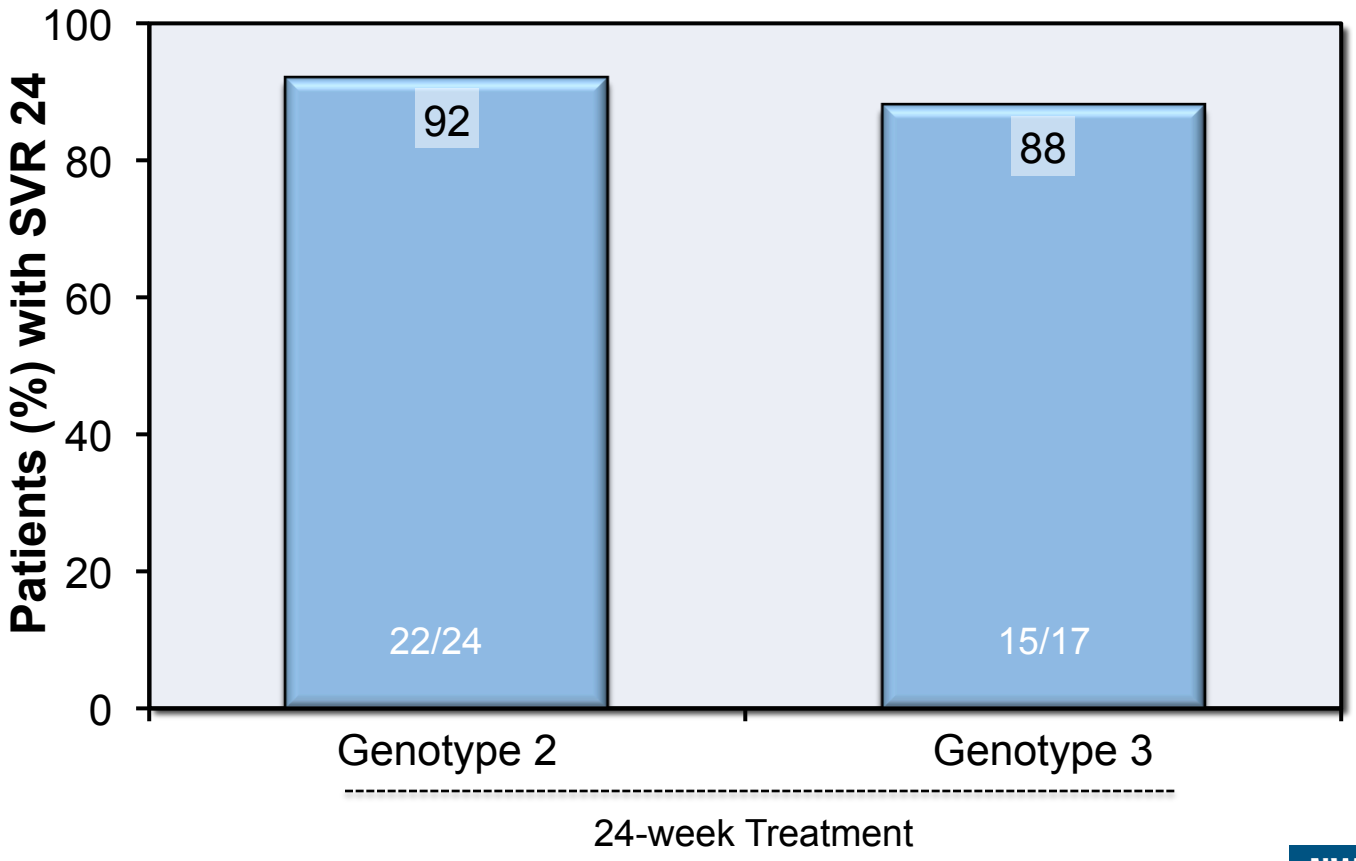
Sofosbuvir and Ribavirin for HCV-HIV Coinfection
PHOTON-1: Results for Treatment-Experienced Patients

PHOTON-1: SVR 24 HCV RNA <25 IU/ml



Naggie S, et. al. CROI 2014. Abstract 26.

PHOTON-1
HCV Virologic Failure – No major resistance

- Viral relapse was main way patients failed to achieve SVR (39/41).
- The 2 patients with viral breakthrough had no detectable sofosbuvir level, suggesting non-adherence
- No S282T variants detected
- No NS5B polymorphisms conferring phenotypic resistance

Naggie S, et. al. CROI 2014. Abstract 26.

PHOTON-1
Adverse Events

	SOF + RBV 24 weeks (n=155)	SOF + RBV 12 weeks (n=68)
Grade 3-4 Adverse events	12	10
Serious AEs	6	7
Discontinuation due to AE	3	4
Fatigue	39	35
Insomnia	15	21
Headache	14	13
Nausea	15	18
Anemia Hgb <10 mg/dl Hgb <8.5 mg/dl	 17 1	 10 1

HIV Safety: n=2 on ART with transient HIV viremia with documented non-adherence
No decrease in abs/% CD4 cell counts

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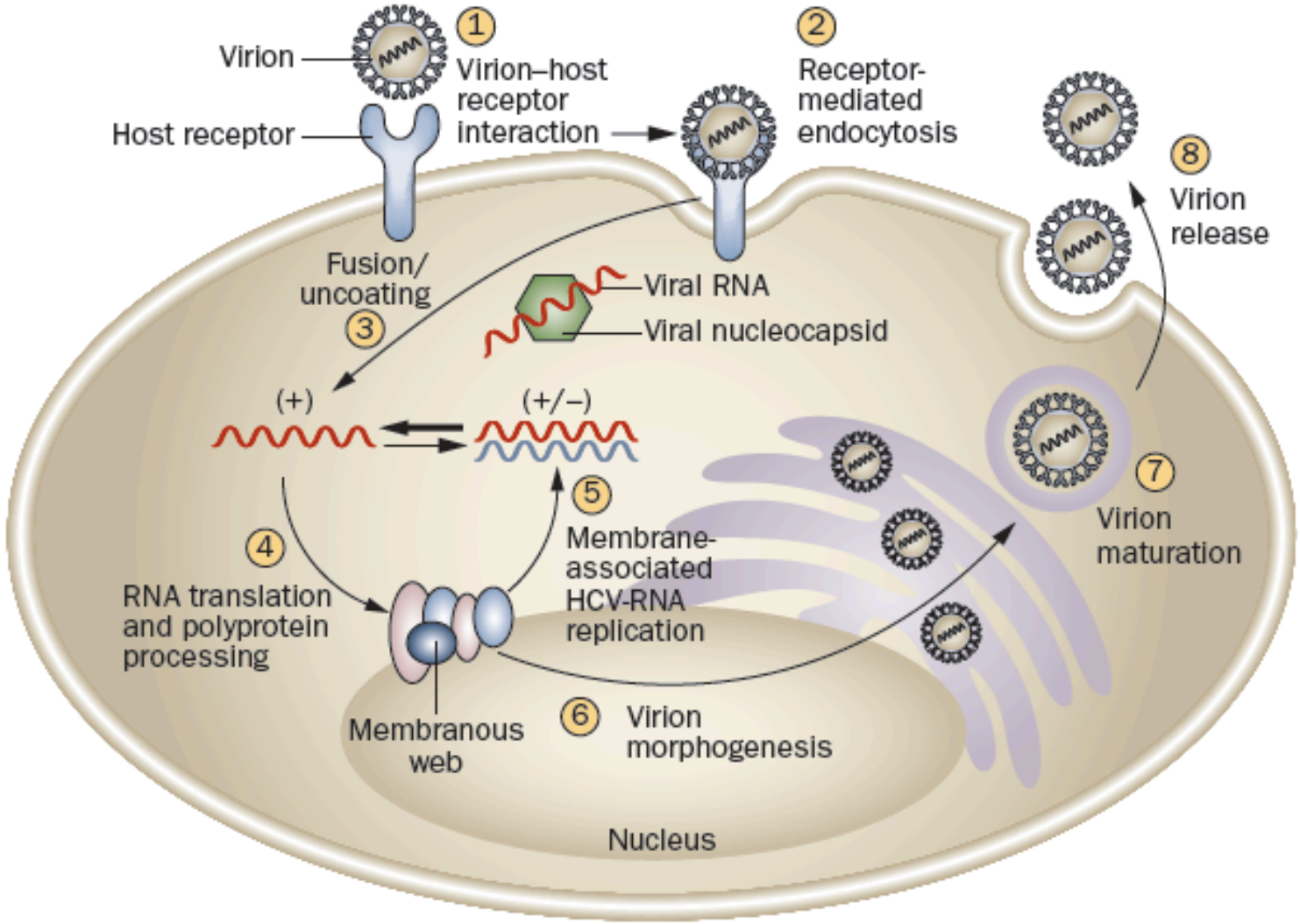
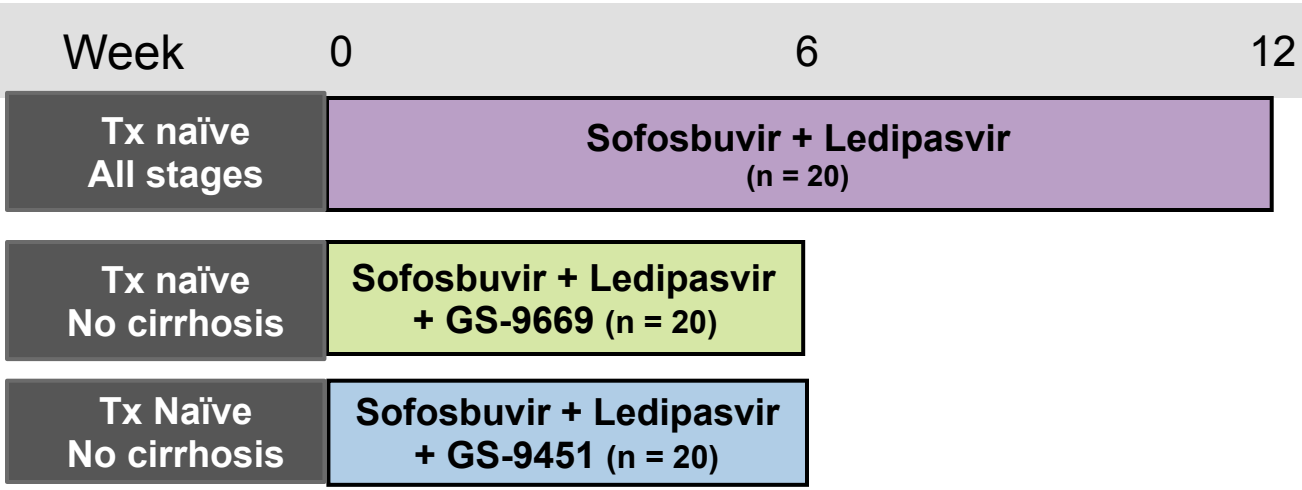
HCV Targets for Direct-Acting Antivirals (DAAs)



Pereira AA, et. al. *Nat Rev Gastroenterol Hepatol*. 2009; 6:403-411.

NIH SYNERGY Trial
Can we shorten HCV therapy to 6 weeks?

- Objective: To use multiple DAAs targeting different stages of HCV lifecycle to shorten duration necessary to achieve SVR
- Triple all-oral interferon-free combination in HCV monoinfected:
  - Sofosbuvir (NS5B inhibitor)/ledipasvir (NS5A inhibitor) 400/90 mg once daily
  - GS-9669 (non-nucleoside NS5B inhibitor) 500 mg once daily
  - GS-9451 (NS3/4 A protease inhibitor) 80 mg once daily



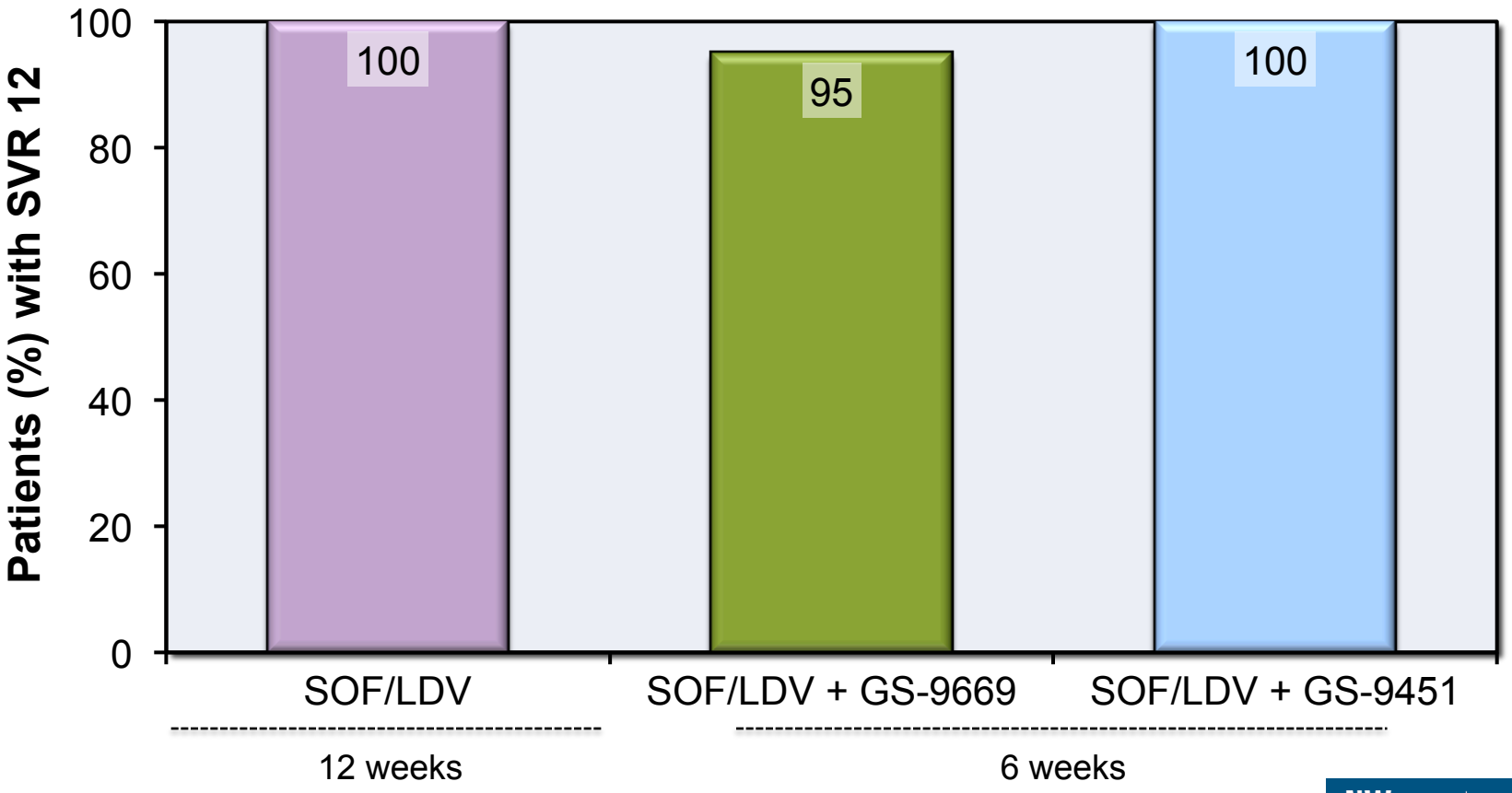
Kohli A, et. al. CROI 2014. Abstract 27LB.

NIH SYNERGY
Participants

	SOF/LDV 12 wks (n=20)	SOF/LDV + GS-9669 6 wks (n=20)	SOF/LDV + GS-9451 6 wks (n=20)
Age, mean	57	54	54
Male, %	70	65	80
Black, %	80	95	90
HCV genotype, % 1A 1B	 55 45	 70 30	 85 15
IL28B CT/TT, %	75	90	75
Advanced fibrosis, % Knodell score 3 Knodell score 4	 25 15	 25 0	 25 0

Kohli A, et. al. CROI 2014. Abstract 27LB.

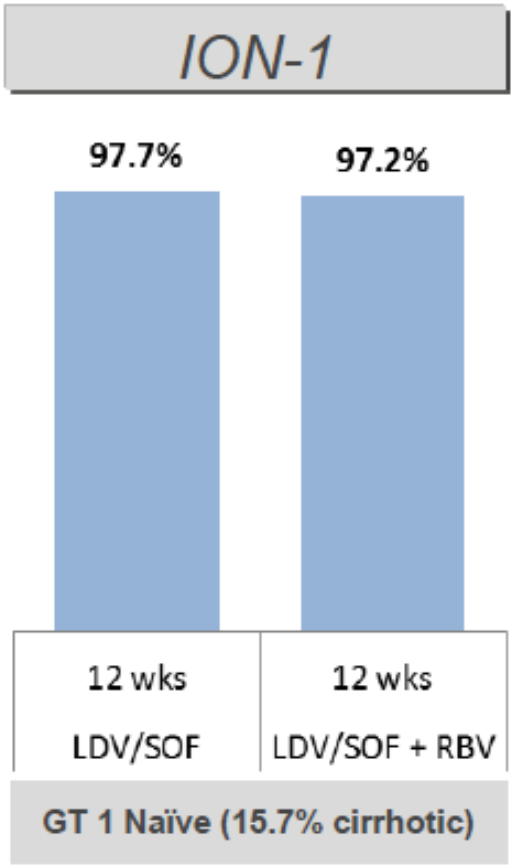
NIH SYNERGY
Treatment Response



Kohli A, et. al. CROI 2014. Abstract 27LB.

Interferon-free HCV Therapy

- Proof of concept – it is effective in HIV-infected patients with SVR rates similar to HCV monoinfected patients
- Multi-mechanism combinations may allow duration of therapy as short as 6 weeks
- ION-4 – Sofosbuvir/ledipasvir in HCV-HIV coinfected patients



U.S. lawmakers want Gilead to explain Sovaldi's hefty price

BY BILL BERKROT AND DEENA BEASLEY

Fri Mar 21, 2014 4:56pm EDT

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Health »

(Reuters) - U.S. lawmakers have asked Gilead Sciences Inc to explain the $84,000 price tag of its new hepatitis C drug Sovaldi, which is encountering resistance from health insurers and state Medicaid programs.

FIB-4 outperforms Liver Biopsy as Predictor of Death or Liver-related Events

- N=903 HIV-HCV coinfected patients in the GESIDA cohort (Spain)
- After median 63 months, 46 died and 71 had liver-related event (decompensation or HCC)

	Adjusted Hazard Ratio (95% CI)	P-value
Death		
Liver biopsy (≥F3 vs <F3)	1.76 (0.84-3.69)	0.136
FIB-4 (≥3.25 vs <3.25)	**4.26** (0.95-18.2)	0.051
Liver-related Events		
Liver biopsy (≥F3 vs <F3)	2.37 (1.44-3.90)	0.001
FIB-4 (≥3.25 vs <3.25)	**4.34** (2.65-7.11)	<0.001

FIB-4 = (Age [years] x AST [IU/L]) / (Platelets [10^9/L] x (ALT [IU/L])$^{1/2}$)

Berenguer J, et. al. CROI 2014. Abstract 640.

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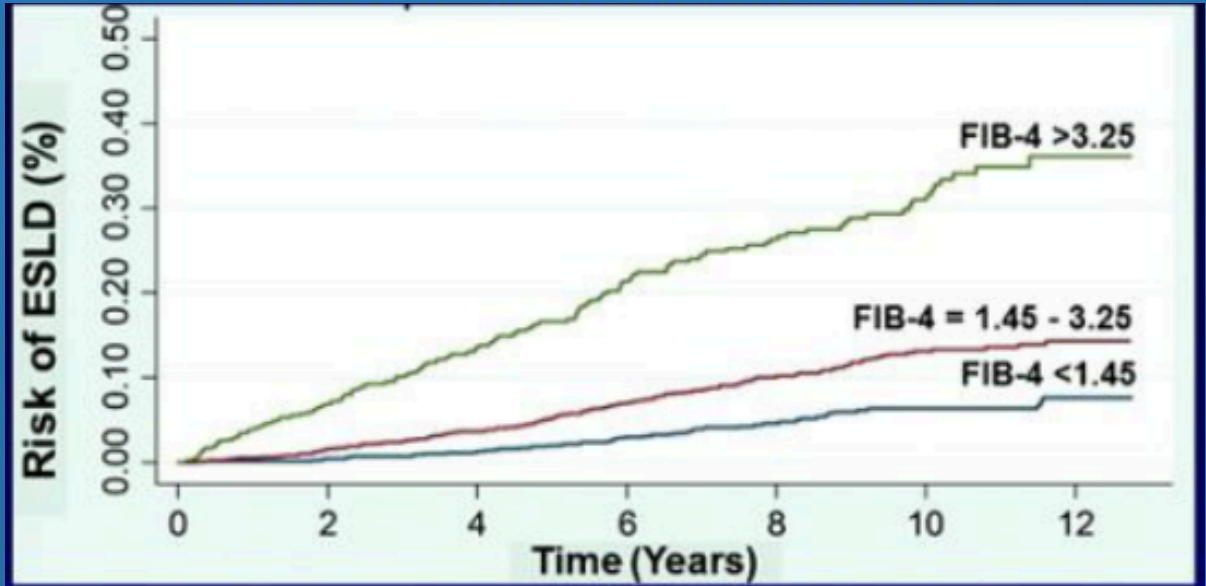
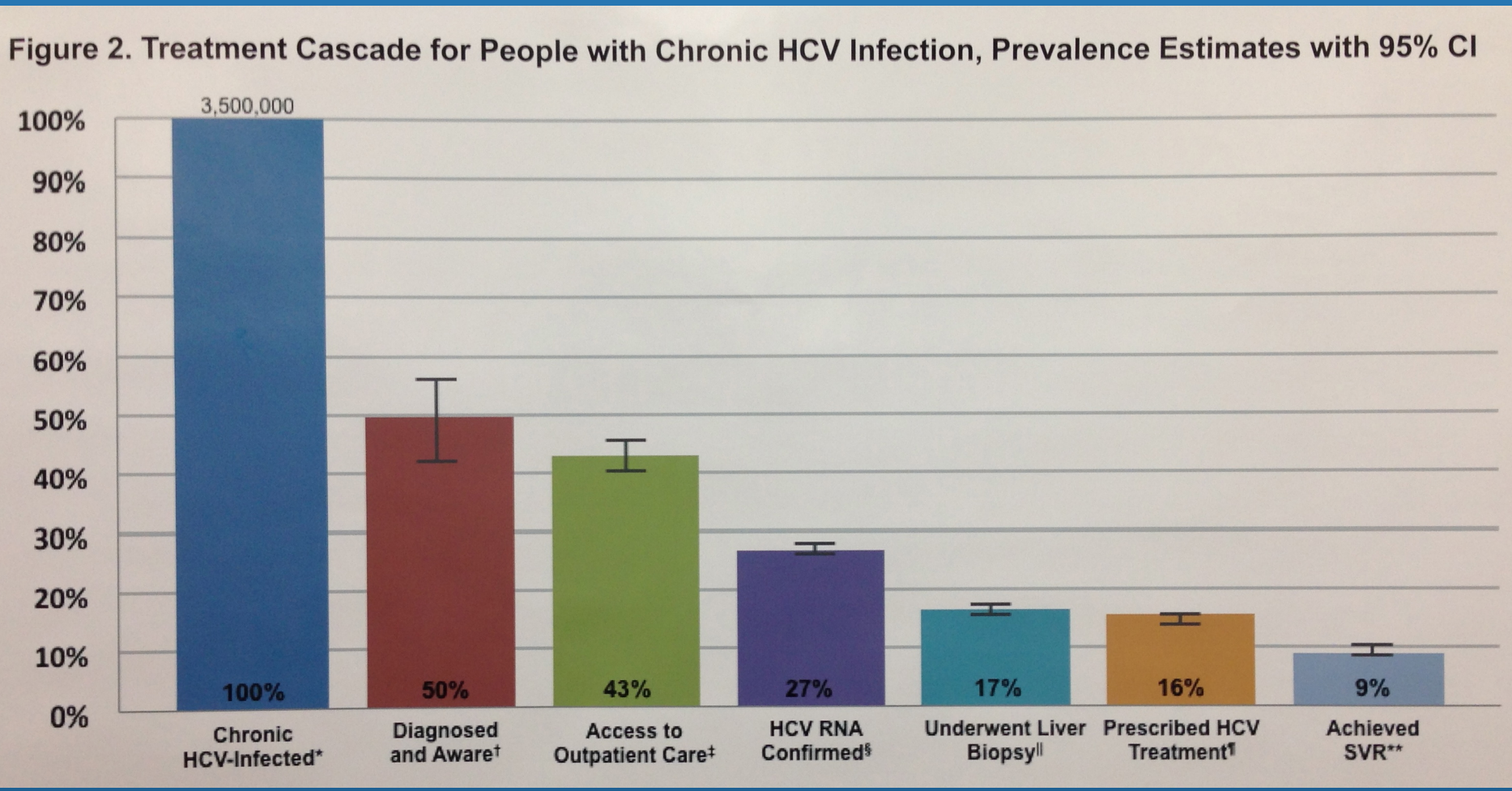
Risk of End-stage Liver Disease by FIB-4
VACS Cohort



FIB-4 Score	Risk of ESLD at Specified Time				
	1 Yr	3 Yrs	5 Yrs	7 Yrs	9 Yrs
<1.45	0.1%	1%	2%	4%	6%
1.45-3.25	0.6%	4%	5%	9%	12%
>3.25	4%	10%	17%	25%	29%

LoRe V, et. al. CROI 2014. Abstract 650.

Hepatitis C Care Cascade



Yehia B, et. al. CROI 2014. Abstract 669.