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The AIDS Institute's Deconstructing Hepatitis C Treatment Webinar

July 9, 2014

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Webinar Logistics

The webinar is being recorded.

All lines are muted to reduce background noise.

Questions may be asked at the end by virtually “raising your hand.”

You must enter your AUDIO PIN to be able to speak.

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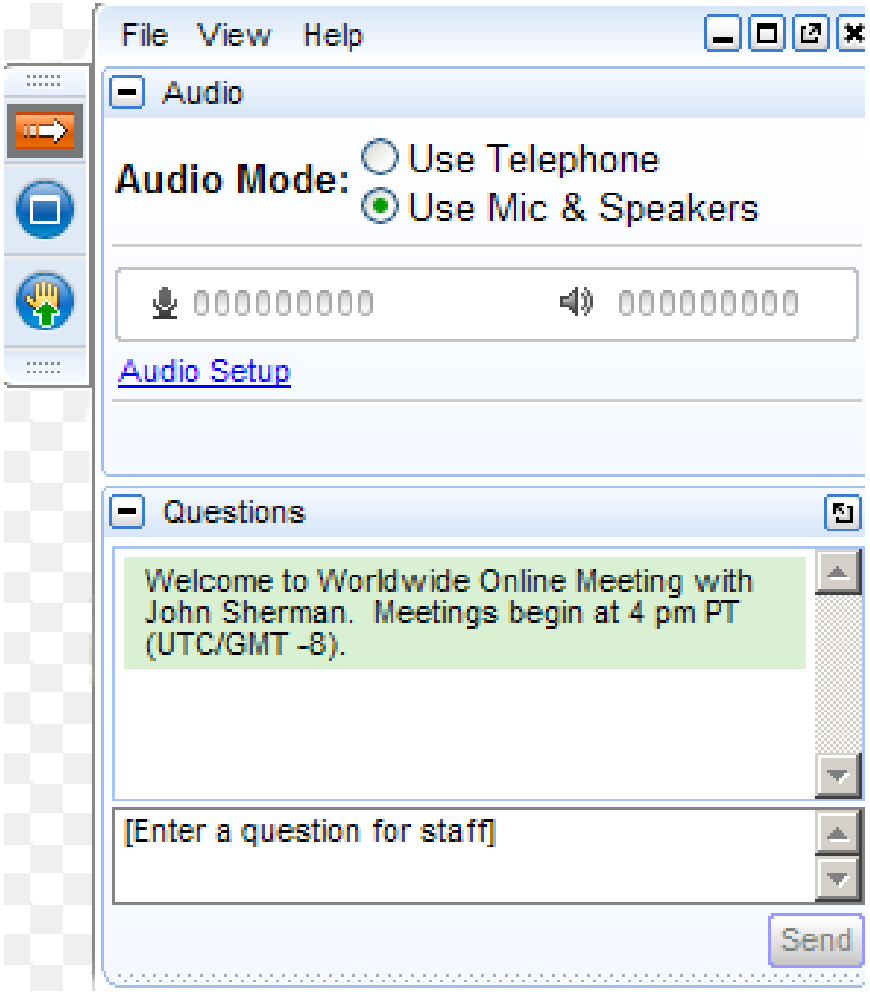
Questions

Questions may be asked by virtually "raising your hand." All lines are muted until individuals are called upon.

Your "hand" is raised when a red arrow is present.
Your "hand" is down when a green arrow is present.



<u>You must enter your AUDIO PIN</u>
<u>to be able to speak.</u>

Deconstructing HCV Treatment builds on The AIDS Institute's series of hepatitis related webinars. Therefore, HCV material will be more intricate.

Please help us shape future educational webinars by completing the 5-question survey immediately following the webinar.

July 28 is World Hepatitis Day.

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Philip Styne, M.D., AGAF
(American Gastroenterological Association Fellow)
Medical Director, Digestive Health & Clinical Informatics
Florida Hospital
Orlando, FL

Dr. Styne will present on:

- Current HCV Treatments
- Barriers To Treatment and Adherence
- Treatment As Prevention

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Tracy Swan
Hepatitis/HIV Project Director
Treatment Action Group
New York, NY

Ms. Swan will present on:
HCV-HIV Co-Infection

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Hepatitis C Treatment Deconstruct

Philip N Styne M.D. AGAF
Medical Dir. Digestive Health and Clinical Informatics
Florida Hospital Orlando

Financial Disclosure

- Gilead
- Salix
- Bristol Myers-Squibb
- Bayer
- These are on-going drug studies including Hepatitis C

Hepatitis C Treatment Deconstruct

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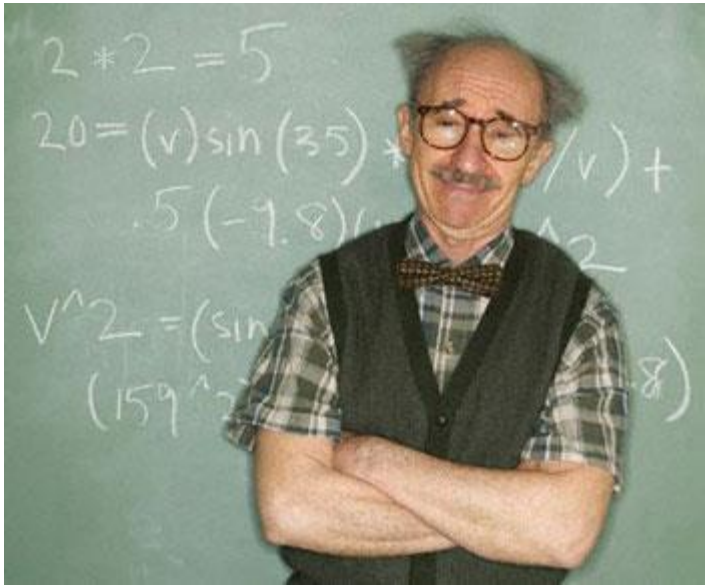
There is always a decision of who to treat for any disease:

There is an equation that takes into account the difficulty of treatment/ likelihood of serious consequences of non treatment/ cost of non treatment/ effectiveness/ cost of treatment/ side effects.

The Decision Equation

(DT X SCNT ($ ESC) × 👌 × ⌛ ÷ $Rx × SE) × 📠💻 = to treat or not to treat (that is the question)



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There really is an equation for this…

Incremental cost-effectiveness ratio (**ICER**)

$=$ Net Cost

difference in lifetime costs between strategies)

$\div$ Net Benefit

benefit (difference in life expectancy or quality-adjusted life expectancy between strategies)

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Hepatitis C:

Journey From Non-A Non-B Hepatitis to Cure

- Non-A non-B was mostly associated with post-transfusion hepatitis though lots of mildly abnormal aminotransferases were attributed to NANB
- Hepatitis B first identified in 1963 and hepatitis A in 1973

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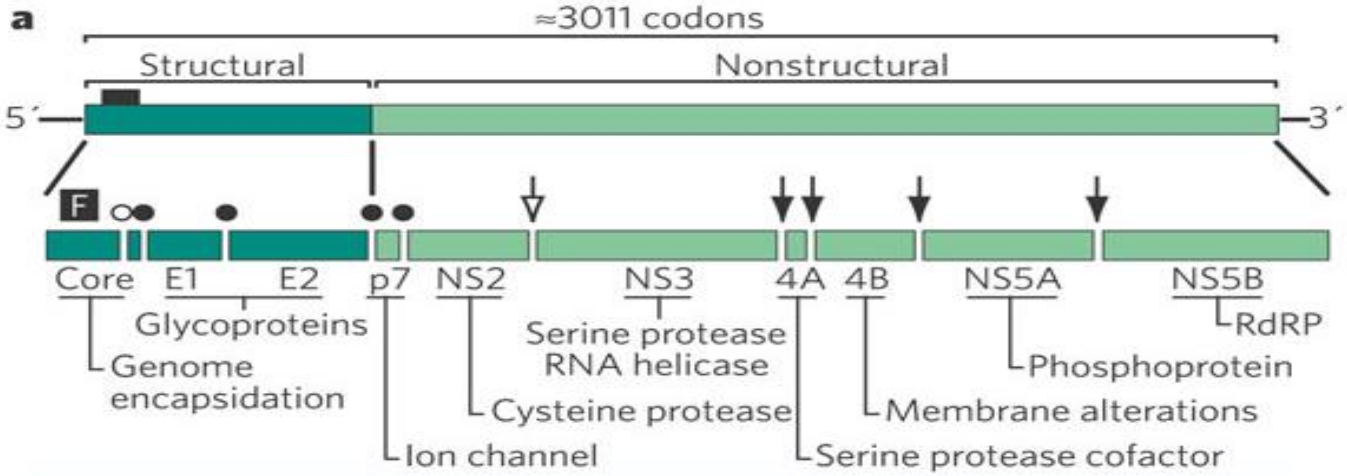
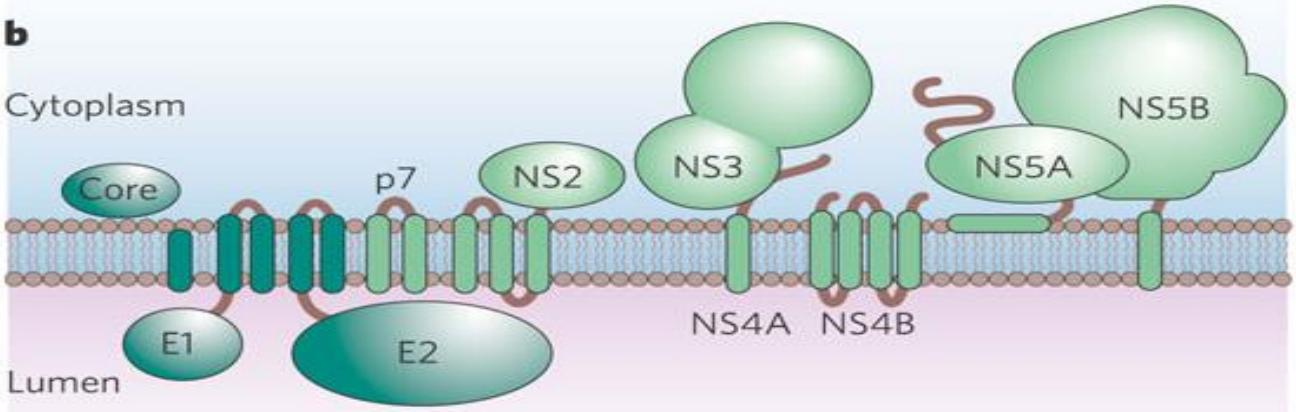
History of Hepatitis C

- 1989-identified hepatitis C virus
- 1990-started blood bank testing
- 1992 blood bank testing perfected
- One difference between these two types of virus is that hepatitis C lacks a prolonged intracellular existence which would protect it from antiviral therapy as hepatitis B has.
- 1990s-first use of interferon SQ ttw (NIH protocol) for treatment of hepatitis C with very poor results especially in countries with high genotype 1 populations
- 1998-addition of ribavirin guanosine analog to interferon as a therapy with some increase in response -pills plus shots
- 2001-interferon modified with PEG to allow once per week dosing with again some gains in response but still SQ

Hepatitis C Genome and How DAAs are Built





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Direct Acting Antivirals (DAA)

- NS3/4 A protease inhibitor -***PI***
- NS5B nucleoside polymerase inhibitor- ***NPI***
- NS5B non-nucleoside polymerase inhibitor – ***NNPI***
- NS5A inhibitor- ***NS5AI***

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Therapeutic Break-Through

- 2011-first DAA
- Telaprevir/boceprevir :
  - still long therapy
  - still requiring interferon and ribavirin
  - lots of side effects
  - complicated regime requiring frequent testing and dose modification and very expensive
- $189,000 per SVR

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Therapeutic Advances

- 2013- release of new direct acting agents simeprevir NS3/4 PI and sofosbuvir NS5B PI but still with interferon except genotype 2 and and maybe 3
- 2014- AASLD and IDSA release broad recommendations many off label therapies (sof/sim)
- 2014- additional DAA expected from Gilead to be interferon free for geno 1 sofosbuvir and ledipasvir NS5AI (sof/le) the combination of a NS5B PI and NS5AI
- 2015- additional DAA from Abbvie 3D ABT 450 a PI plus ritonavir plus dasbuvir NNPI plus ombitasivir a NS5AI for interferon free therapy

Due to a Change in ICER…

- 2012- CDC recommends screening those born 1945-1965
- 2013- USPTF recommends similar screening

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What is the big deal?

- Liver disease 10th cause of death in US
- 3.2 million with hepatitis C in the US
- $1 billion total cost per year

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Keeping up with the Research

A myriad of studies that require constant updating in current and potential therapies.

- Prove
- Realize
- Illuminate
- HCV Sprint
- Respond
- PEARL
- COSMOS
- Neutrino
- Valence
- HALT C

Major Concerns with Cost

Cost of therapy must be weighed against cost of non treatment both in dollars and QOL.

- Telaprivir $189000 per SVR - no uproar for the full therapy
- Sofosbuvir $85,000 for a three month course
- End stage liver disease - average cost of single admission for variceal bleed $50-$75,000
- 1991-1995 $39,000-$222,000 per patient hospitalization with 37% spent on patients who died
- Cirrhosis $24,000-$38,000 per year 1995 dollars
- Liver transplant first 3 months cost $250,000

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Complicated Testing and protocols

Soon to be a thing of the past

- Genotype will be using but G 3 is the new G 1
- IL 28 probably will be irrelevant
- Q80K already old news
- RVR EVR will no longer be measured

Natural History of Hepatitis C

If this were better defined, we would be able to make better decisions in terms of treatment.

- Acute hepatitis C-rarely symptomatic-most likely infectious sexually
- 80% develop chronic hepatitis
- Chronic hepatitis C 20-40% becoming cirrhotic after 2-3 decades
- Cirrhosis accelerated in time, frequency and subsequent decompensation by alcohol and HIV

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Establishing Disease State & Predict Advancement

- Liver biopsy – not perfect because of sampling error
  - Grade=inflammation
  - Stage= scaring
  - Be aware of different scales 0-4 vs 0-6
- Blood tests – Fibrosure good at extremes of scaring; poor at prediction
- Percussive – FibroScan

Who Should be Tested?

- All those born between 1945 in 1965
- Abnormal aminotransferases
- History of IV drug use
- History of transfusion prior to 1992
- History of clotting factor prior 1987
- Sexual contact with IV drug user or hepatitis C patient
- HIV patient
- Dialysis patient
- Healthcare needle stick recipient and if possible donor
- Incarcerated individuals

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To Treat or not to Treat…

- Not all patients develop cirrhosis
- It often times is difficult to determine who will and who will not develop cirrhosis
- The addition of alcohol in patients with hepatitis C is a common problem
- Extra hepatic complications often indication for therapy

Extra Hepatic Manifestations

- Depression and fatigue
- Porphyria cutanea tarda
- ITP
- Renal disease
- Vasculitis
- Thyroid disease
- Non-Hodgkin's B-cell lymphoma
- Essential mixed cryoglobulinemia

That is the Question

- The decision to treat changes with each new option for treatment and information about the disease
- With each new treatment there may be higher percentage of cure, lower side effects, increased cost and an increased patient pool

Cirrhosis

What we are trying to prevent

- Scarring and disruption of normal architecture of liver
- Decompensation
  - Variceal bleed esophagus and stomach
  - Ascites
  - Spontaneous bacterial peritonitis
  - Hepatic encephalopathy
  - Hepatorenal syndrome
  - Hepatopulmonary syndrome
  - Hepatocellular carcinoma

Barriers To Treatment

- Well known side effects and long duration of therapy
- SHOTS!!! I give myself!!!
- Stigma of diagnosis especially in the baby boomers (my boss at the bank would know I was a IVDU)
- Cost $$$$
- The boomers often fall into a insurance gap between work ending and Medicare beginning.

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A Patient you might not treat:

(will probably never have complication)

- 76 yo WF got transfused at age 30 during complicated delivery
- Dx with hepatitis C three years ago Geno 1b RNA 3,000,000
- Bx done three years ago Grade 1 Stage 1 disease
- AST 42 ALT 38 all other lab normal

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A Patient you might treat now or in Oct 2014:

(borderline for cirrhosis)

- 66 yo WM IVDU once in 1970 in VN also drinks ETOH No history of decompensation
- Dx this year Geno 1a RNA 2,000,000
- AST 100 ALT 110 platelet 130,000
- CT lobulated liver- spleen 14cm
- RX Sof/Sim now or Sof/Le in future
- Must quit all ETOH now and forever more

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A Patient you would treat now:

(cirrhotic now)

- 56 yo WM IVDU in past plus ETOH
- Platelet 87,000 albumin 2.9 AST 90 ALT 100
- CT lobulated liver- spleen 18cm-varices
- Decompensated with ascites now controlled with diuretics and off ETOH

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While our journey to *curing* hepatitis C is a long way down the road, we now have an opportunity to drastically reduce the *disease burden*.

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Hepatitis Reduction Strategies

- Reduction in the incidence of hepatitis B has been largely based on vaccine and some reduction in viral load and reduction of the chronic state by anti-viral therapy.
- Reduction in the incidence of hepatitis C has been largely based on viral eradication especially in those likely to transmit based on their personal activates. There is no vaccine for hepatitis C.

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From a public health standpoint, reducing the *burden* of the hepatitis C virus can lessen the *incidence*.

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Hepatitis C Treatment in HIV/HCV Coinfection

The AIDS Institute
July 2014

Tracy Swan
Treatment Action Group

TAG
Treatment Action Group

Overview

Epidemiology of HIV/HCV

Natural History of HIV/HCV

SVR with PEG-IFN-based treatment

SVR with DAAs

Special Considerations

Epidemiology: HIV/HCV

- In the United States, up to 30% of all HIV+ people are HCV-coinfected
  - Rates among HIV+ PWID are much higher—up to 90%
- Outbreaks of sexually transmitted HCV in the U.S., Europe, Australia and Asia among HIV+ MSM have been reported since 2000

Bradshaw, et al; Curr Opin Infect Dis 2013;
Sulkowski MS; J Infect Dis 2013

Natural History of HIV/HCV

- HIV accelerates HCV progression
  - Increases risk for, and rate of cirrhosis
  - HIV significantly worsens survival in people with HCV-associated decompensated cirrhosis

- ESLD secondary to HCV has become a leading cause of death among HIV+ people with access to ART

Graham, et al; Clin Infect Dis 2001; Pineda, et al; Hepatology 2005; Weber, et al; Arch Intern Med 2006

Curing HCV in HIV/HCV

PEG-IFN and RBV: less effective in HIV/HCV, especially G1 (SVR ~25%)

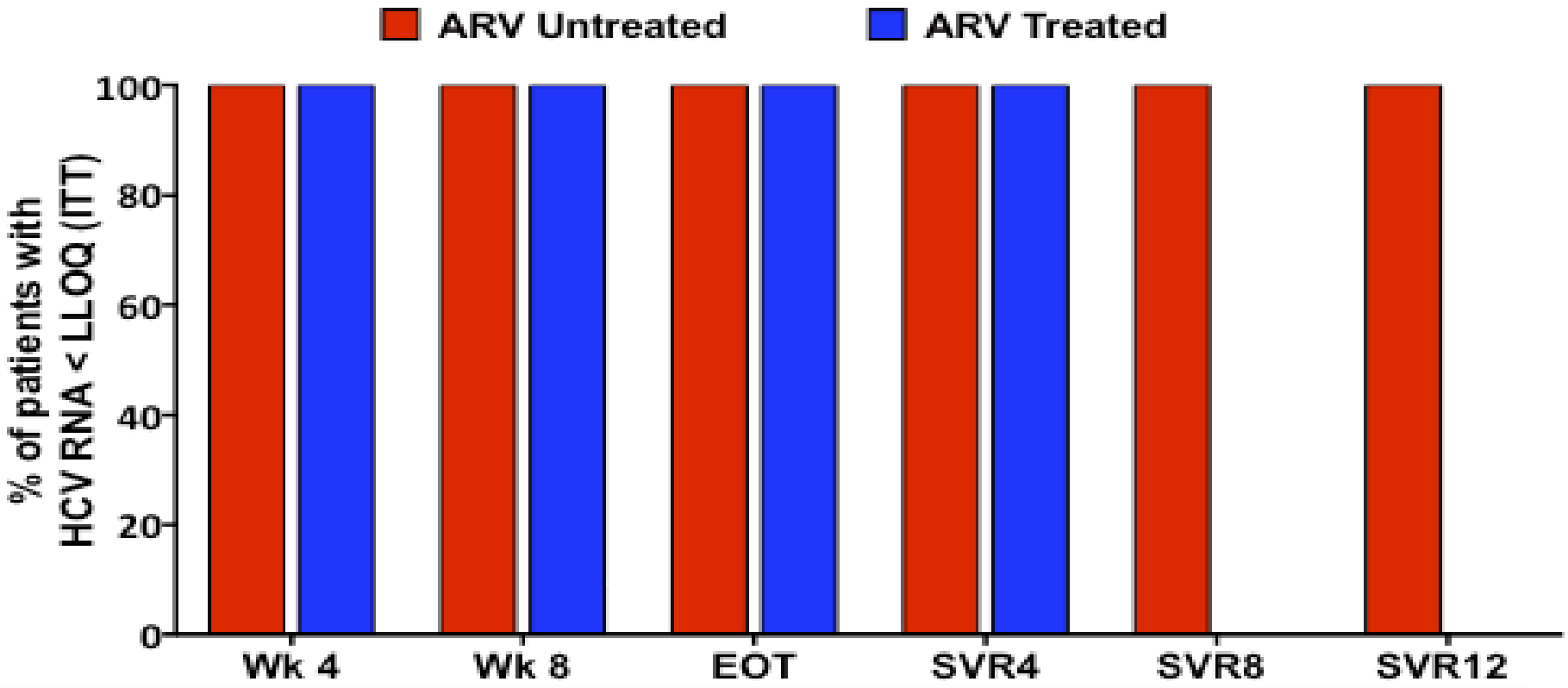
With the addition of an HCV protease inhibitor, SVR rates in G1 do not differ by HIV status

Dieterich et al; EACS 2013; Chung et al; NEJM 2004;Carrat et al; JAMA 2004; Rockstroh et al; AASLD 2013; Sulkowski et al; Ann Intern Med 2013; Sulkowski et al; Lancet Infect Dis 2013; Torriani et al; NEJM 2004

DAAs in HIV/HCV

- PHOTON-1
  - Sovaldi + ribavirin
- ERADICATE
  - Sovaldi/ledipasvir (approval expected in 2014)
- C-WORTHY
  - MK-5172 & MK 8742 ± ribavirin (in phase 3)

ERADICATE: Interim Results



	Wk 4	Wk 8	EOT	SVR4	SVR8	SVR12
ARV -	13/ 13	13/13	13/ 13	12/12	10/10	10/10
ARV +	37/37	37/37	30/30	22/22		

Osinusi et al; EASL 2014

ERADICATE: ARVs

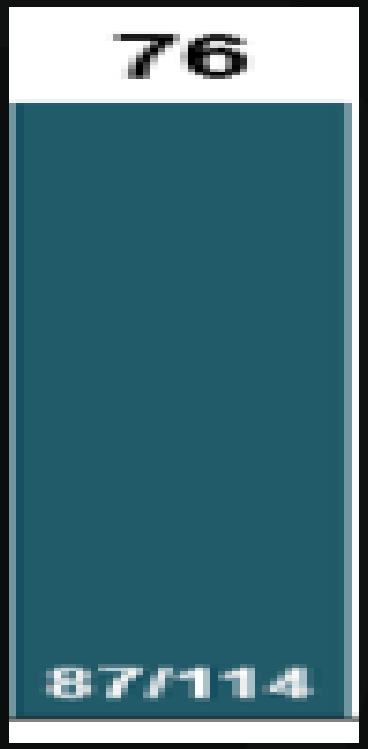
Regimen	ARV Treated n = 37
ARVs n (%)	37 (100)
Tenofovir/Emtricitabine plus	
Efavirenz (EFV)	15 (41)
Raltegravir (RAL)	10 (27)
Rilpivirine (RPV)	8 (21)
RPV/RALT	3 (8)
EFV/RALT	1 (3)

Osinusi et al; EASL 2014

PHOTON-1: HIV/HCV G1

SVR, G1 Sovaldi + ribavirin: SPARE

68%	NIH SPARE Study (24 weeks)

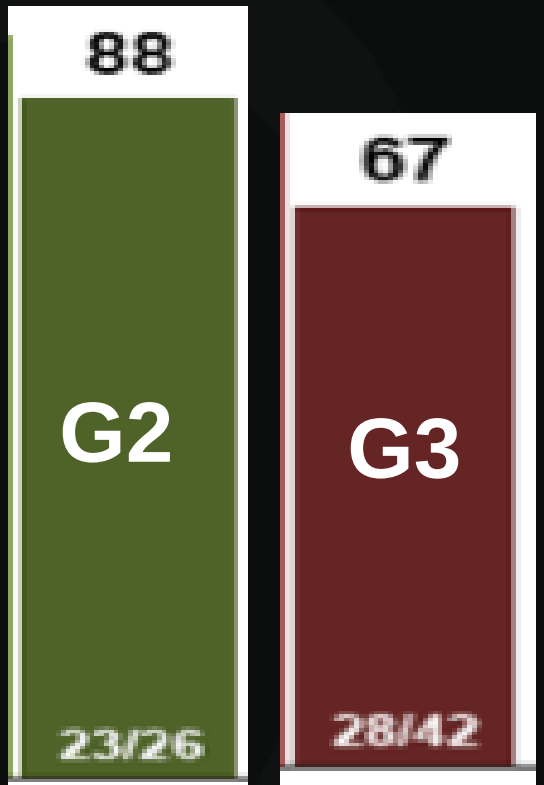


SVR, G1, HIV/HCV
Sovaldi + ribavirin:
PHOTON-1

Osinusi, et al; JAMA 2013; Sulkowski, et al; AASLD 2013

PHOTON-1: HIV/HCV G2 & G3 Sovaldi and ribavirin

GT 2	97%	FISSION Study (12 weeks)
GT 3	56%	FISSION Study (12 weeks)



Lawitz, et al; NEJM 2013; Sulkowski, et al; AASLD 2013

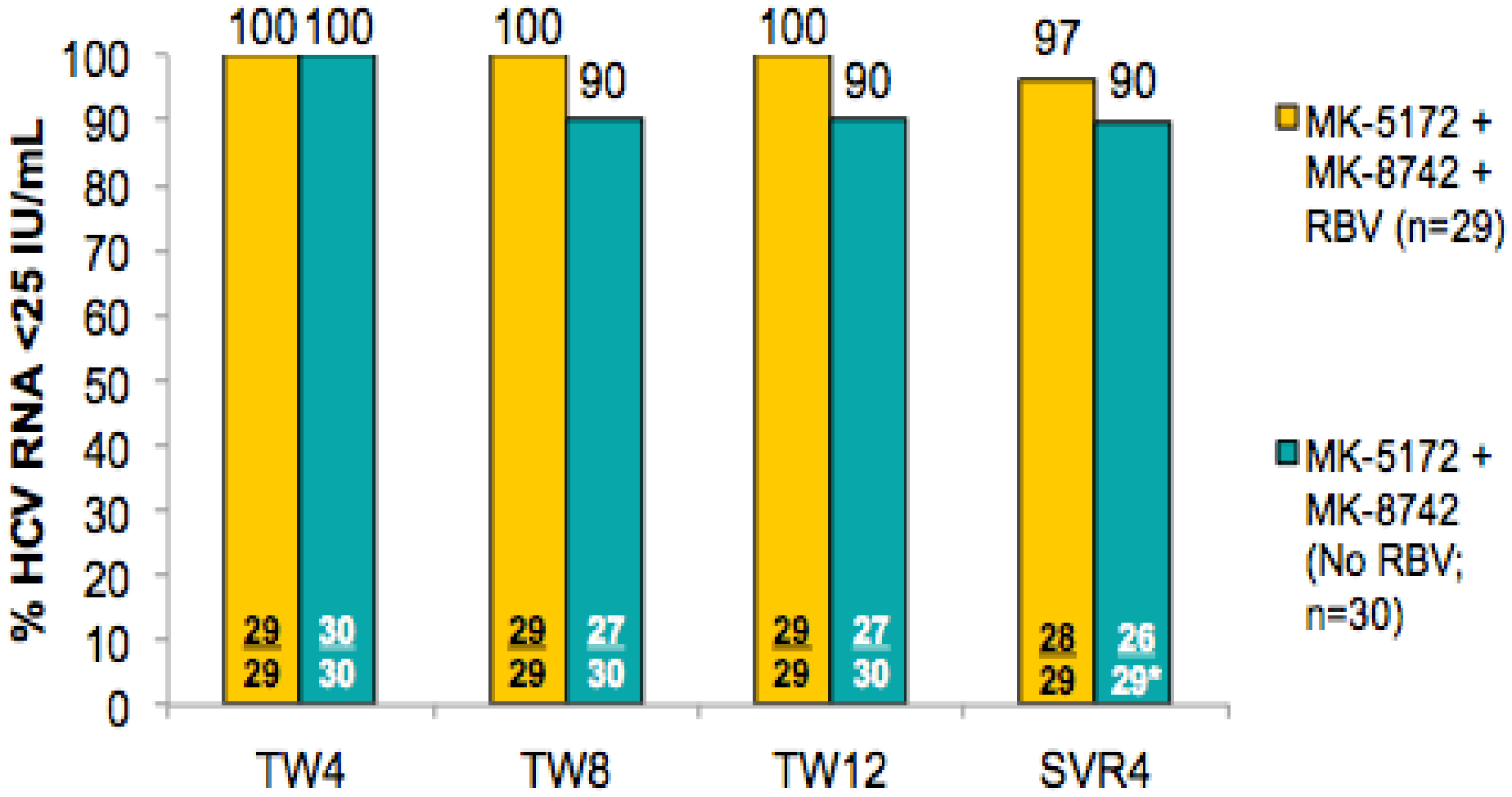
PHOTON-1: ARVs

Regimen, n (%)	SOF + RBV		
	24 Weeks	12 Weeks	
	GT 1 n=114	GT 2 n=26	GT 3 n=42
On ART	112 (98)	22 (85)	39 (93)
Tenofovir DF/emtricitabine **plus**			
Efavirenz	42 (37)	7 (27)	13 (31)
Atazanavir/ritonavir	24 (21)	4 (15)	3 (7)
Darunavir/ritonavir	15 (13)	6 (23)	11 (26)
Raltegravir	21 (18)	2 (8)	6 (14)
Rilpivirine	7 (6)	2 (9)	3 (8)
Other	3 (3)	1 (4)	3 (7)

Sulkowski et al; AASLD 2013

C-WORTHY: HIV/HCV G1

ARVs: raltegravir + 2 NRTIs



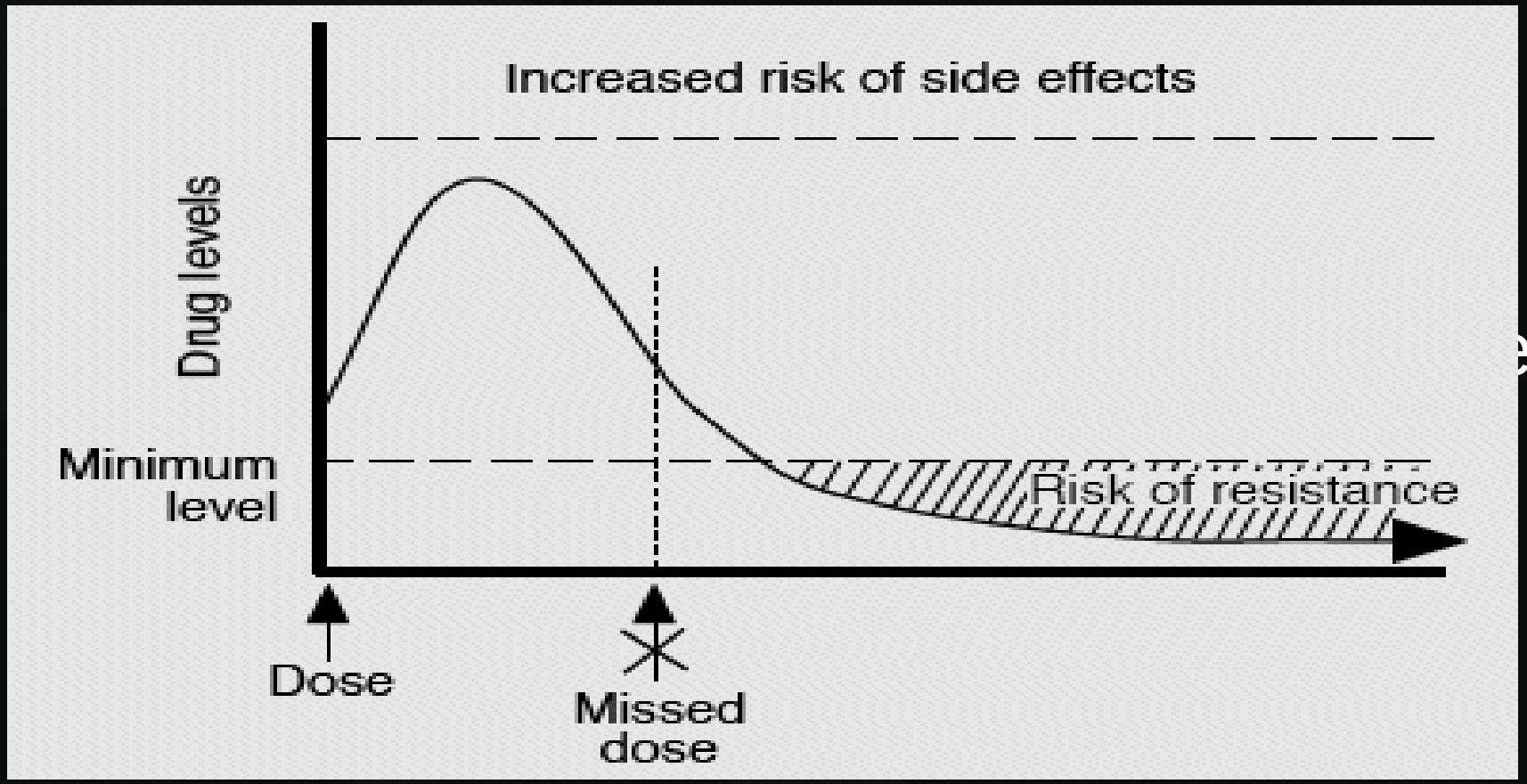
Sulkowski et al; EASL 2014

Challenges: HCV TX in HIV/HCV

- Drug-drug interactions
  - Possible risk of ARV resistance, side effects
- Access to ARV agents that can be co-administered with DAAs
  - Willingness to switch
  - Availability
  - Options for MDR-HIV

Drug pricing…..

Drug-Drug Interactions



http://www.hep-druginteractions.org

The Future: Trials in HIV/HCV, G1

- **ACUTE HCV:** Sovaldi + RBV
- **CHRONIC HCV, G1B ONLY:** Asunaprevir/daclatasvir
- **CHRONIC HCV, TX-NAIVE ONLY:** Sovaldi+ RBV
  MK-5172 and MK-8742
- **CHRONIC HCV, TX-NAIVE or –EXPERIENCED**
  TURQUOISE-1: ABT-450/r/ABT-267 + ABT-333 + RBV
  Asunaprevir/daclatasvir; G1b only
  Sovaldi/ledipasvir FDC
  ALLY-2: Sovaldi + daclatasvir
  Sovaldi/ledipasvir FDC, includes people w/bleeding disorders

Trials in HIV/HCV: G2 and G3

- **ACUTE HCV:**

  Sovaldi + RBV

- **CHRONIC HCV:**

  ALLY-2: Sovaldi + daclatasvir

  Sovaldi+ RBV

HIV/HCV Coinfection

Oral drugs, for 8 to 24 weeks

Cure rates >90%

Fewer side effects

Challenges

Management of drug-drug interactions

Reimbursement/access

Trials in HIV/HCV, G 4, 5 & 6

- **ACUTE HCV:**
  Sovaldi + RBV
- **CHRONIC HCV, G4 ONLY**:
  Sovaldi/ledipasvir FDC, includes people w/bleeding disorders
- **CHRONIC HCV, TX-NAIVE ONLY**:
  Sovaldi+ RBV
  MK-5172 and MK-8742
- **CHRONIC HEPATITIS C, TX-NAIVE and –EXPERIENCED:**
  ALLY-2: Sovaldi + daclatasvir

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E-Learning Webinars “Trends & Topics in Viral Hepatitis”

Mark your calendars!
Future webinar dates include:

Thursday, July 10, 2014 @ 2:00PM (ET)
Coverage of Hepatitis C Testing Under the Affordable Care Act

Wednesday, October 8, 2014 @ 3:30PM (ET)
Topic TBD

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Quarterly HepLink E-Newsletters
Upcoming dates include:
August 1st and November 1st

For more information, visit
hepinfoNOW.org

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