HIV/HCV Co-infection:
An AETC National Curriculum

TREATING HCV INFECTION IN 2019: It doesn't get much better than this

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Disclosures

- Dr. Naggie has received research support from AbbVie, Gilead Sciences, Inc, Tacere; serves as scientific advisor for Vir and BioMarin; serves on event adjudication committee for BMS. (Updated 03/01/2019)
- Discussion of off label use

American Association for the Study of Liver Diseases

AASLD

Recommendations for Testing, Managing, and Treating Hepatitis C

IDSA
Infectious Diseases Society of America

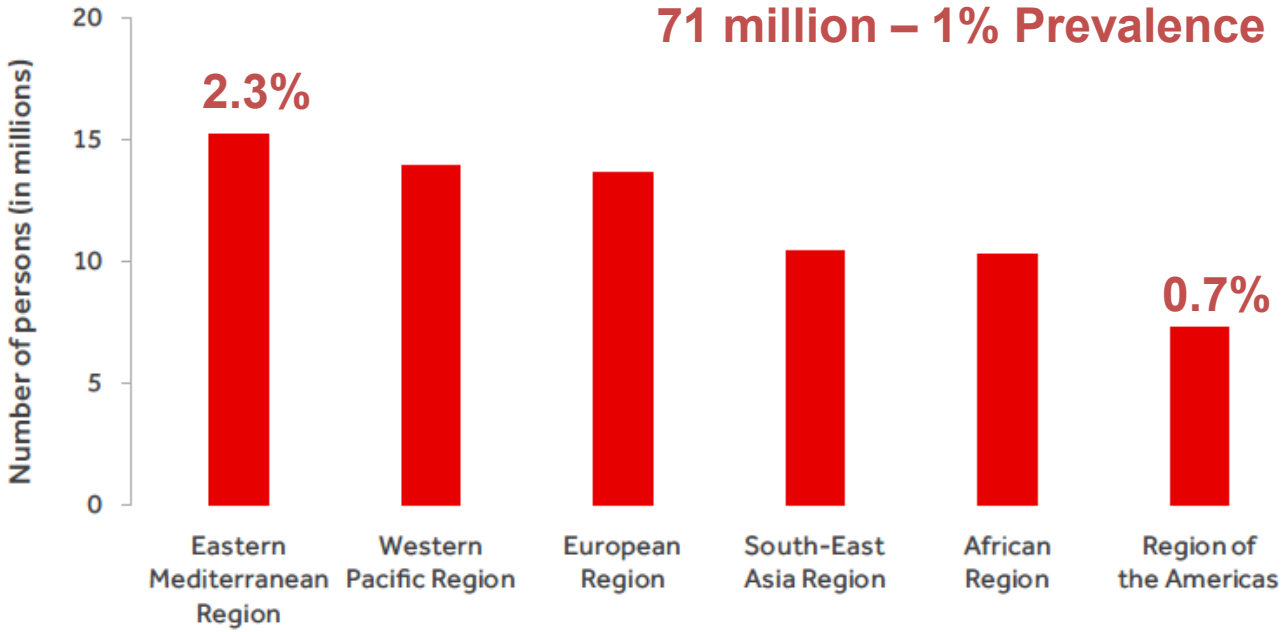
- HCV Introduction
- Testing
- Staging
- HCV Drug Targets and Treatments
- Pre-treatment assessments
- Management post-SVR

www.hcvguidelines.org

Hepatitis C Virus Epidemiology (an update)

Prevalence of Chronic Hepatitis C Infection

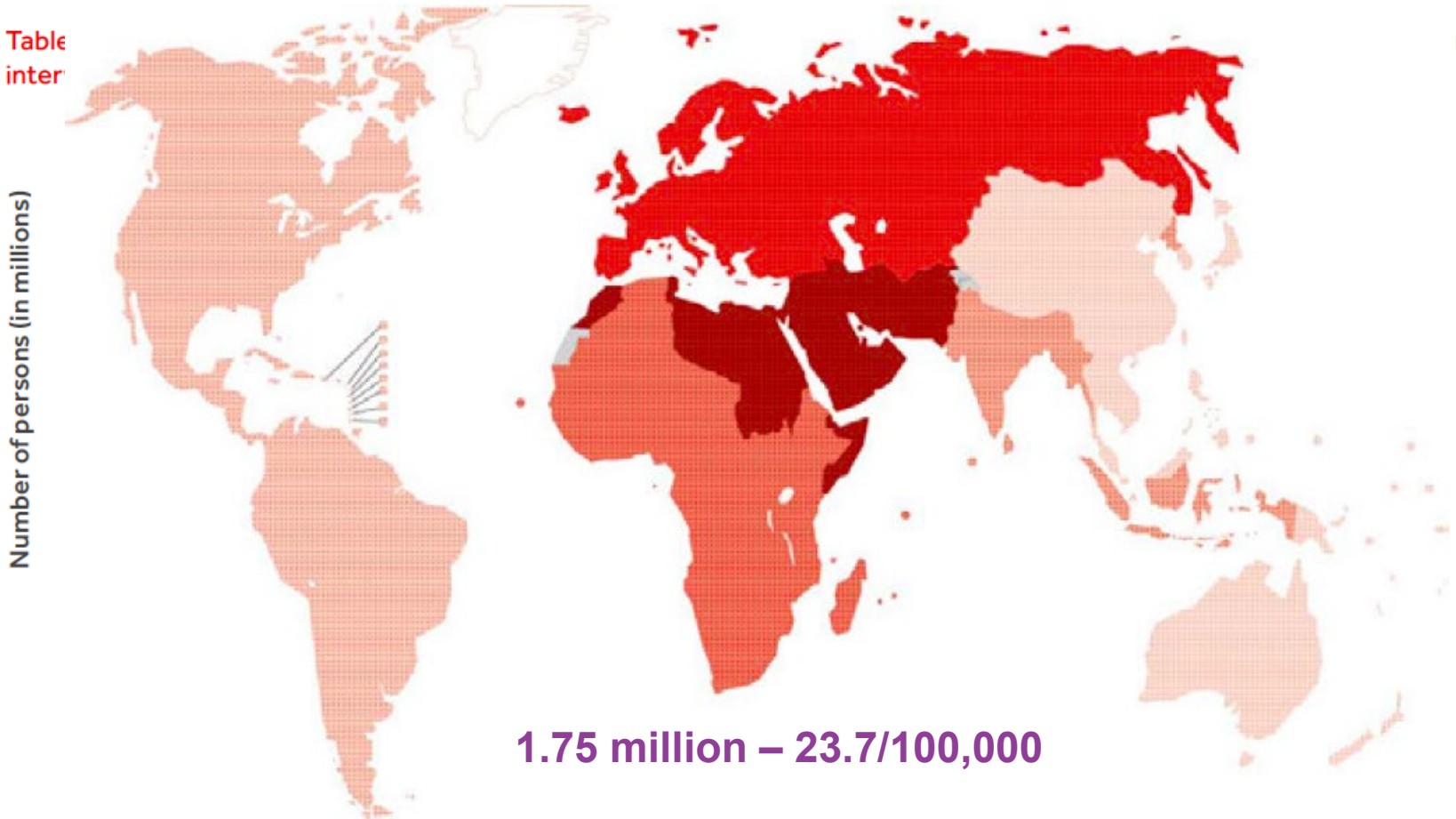
Table 4 (with graph). Prevalence of HCV infection (HCV RNA positive) in the general population, by WHO region, with uncertainty intervals, 2015: 71 million persons living with HCV worldwide



WHO Global Hepatitis Report 2017

Prevalence of Chronic Hepatitis C Infection

Table 3 (with map). Incidence of HCV infection in the general population, by WHO region, 2015: 1.75 million new infections in 2015

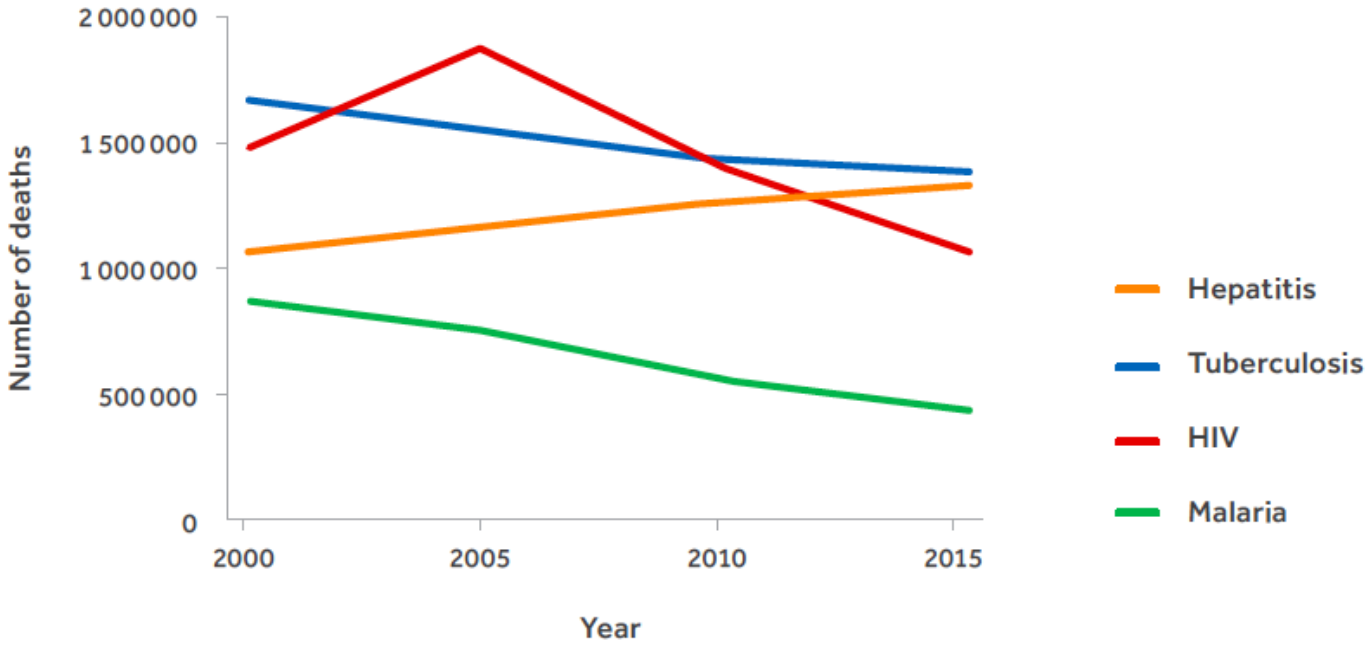


1.75 million – 23.7/100,000

WHO Global Hepatitis Report 2017

HCV – Leading ID Cause of Death Globally

Fig. 2. Global annual mortality from hepatitis, HIV, tuberculosis and malaria, 2000–2015: unlike HIV, tuberculosis and malaria, the trend in mortality from viral hepatitis is increasing

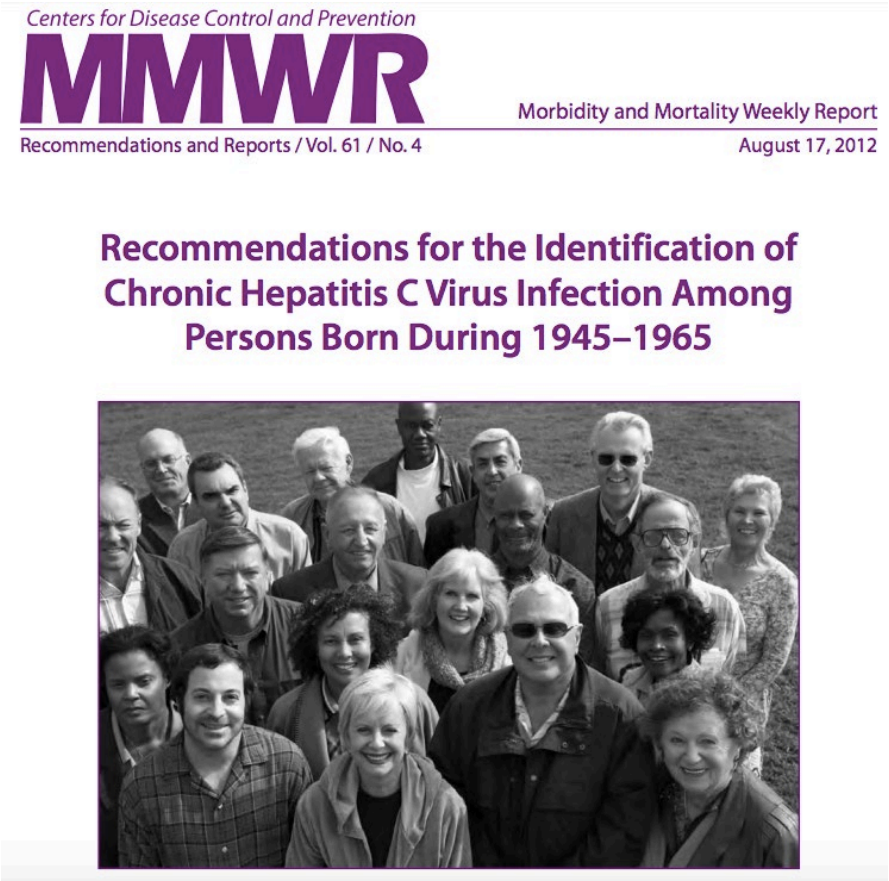


Source: WHO global health estimates (Global Health Estimates 2015: deaths by cause, age, sex, by country and by region, 2000-2015. Geneva: World Health Organization; 2016.)

WHO Global Hepatitis Report 2017

HCV Screening and Testing

HCV Screening



Risk Based HCV Testing

Risk Behaviors

Risk Exposures

Other Conditions and Circumstances

One Time HCV Testing

For persons born from 1945 to 1965 without prior ascertainment of risk

MMWR August 17 2012
www.hcvguidelines.org

Sexual Transmission of Hepatitis C Virus Among HIV-Infected Men Who Have Sex with Men — New York City, 2005–2010

Repeat HCV Testing

People who inject drugs – annually

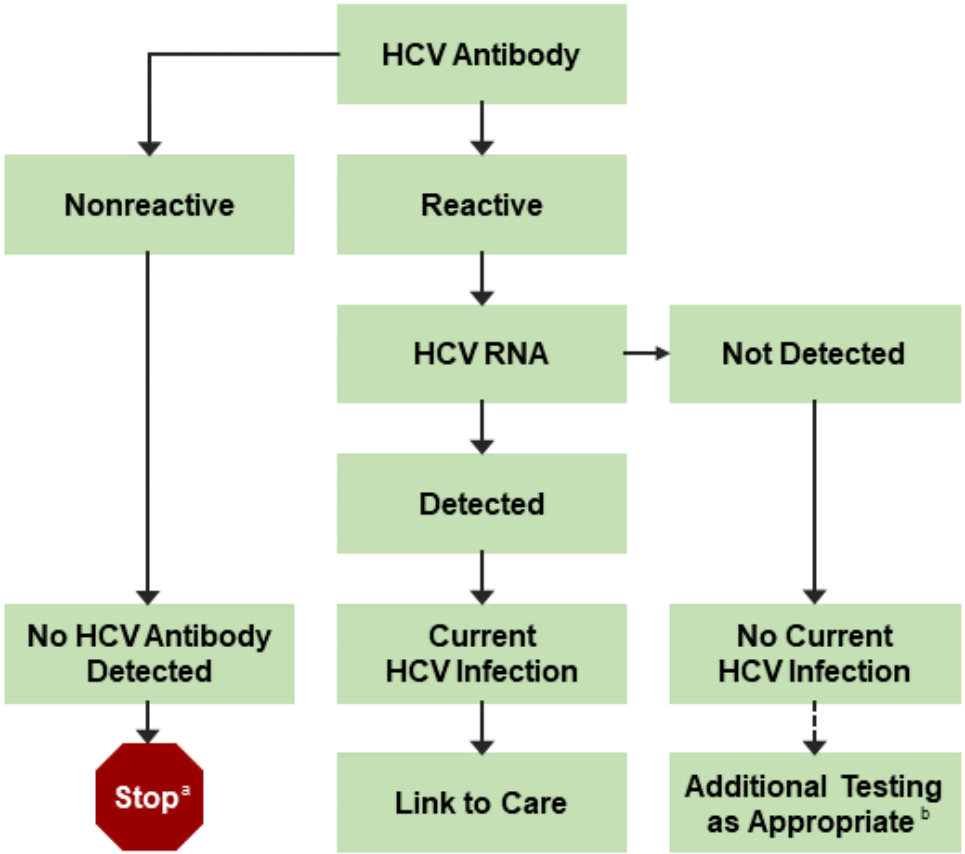
MSM with HIV and high risk – annually

Other risk – frequency based on risk

MMWR July 22, 2011
CDC STI GL 2015

HCV Algorithm

- If previously exposed start at HCV RNA
- Anti-HCV can be rapid (POC) or laboratory based
- If at risk of recent exposure repeat testing in 6 months
- 10-15% rate false negative anti-HCV in immunocompromised



www.hcvguidelines.org

Centers for Disease Control and Prevention (CDC), 2013 (CDC, 2013)

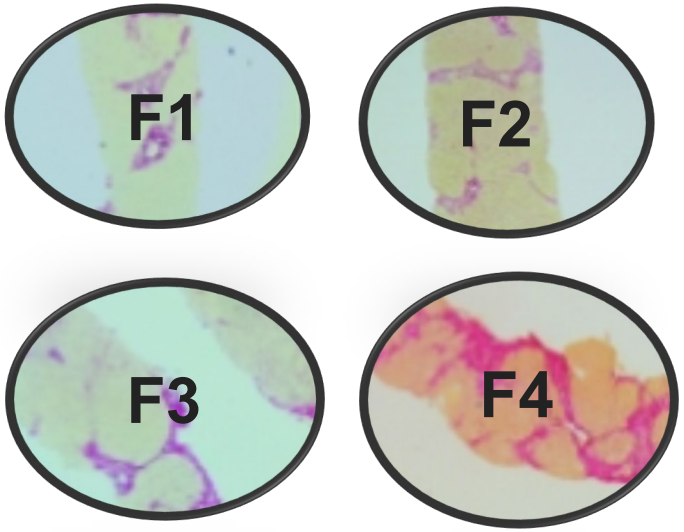
Staging Liver Disease – Still Necessary?

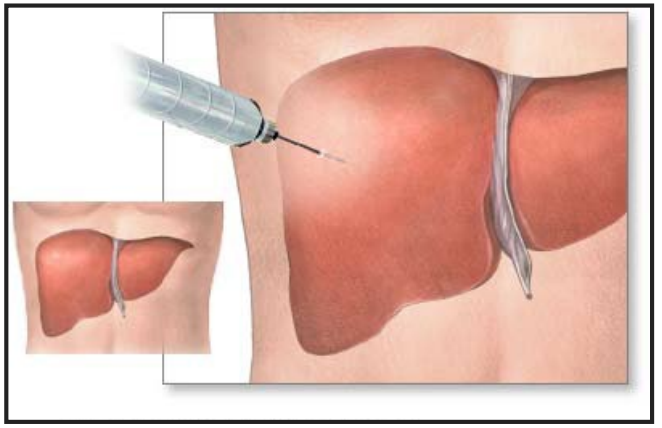
Staging of Liver Disease Still Matters

Recommendations for Pretreatment Assessment

- **Evaluation for advanced fibrosis using liver biopsy, imaging, and/or noninvasive markers is recommended for all persons with HCV infection, to facilitate an appropriate decision regarding HCV treatment strategy and to determine the need for initiating additional measures for the management of cirrhosis (eg, hepatocellular carcinoma screening). (see HCV Testing and Linkage to Care)**

  Rating: Class I, Level A





Rockey DC, et al. *Hepatology.* 2009;49:1017-1044.
Regev A, et al. *Am J Gastroenterol.* 2002:2614-2618.

Alternatives to Liver Biopsy

- Noninvasive approaches
  - Serum Markers
    - Standard laboratory tests: APRI (<0.3,>2), FIB-4 (>3.25)
    - Commercial assays (FibroSure) (>0.8)
  - Serum Markers
    - Elastography
- Limitations
  - Ability to distinguish F1 versus F2, etc.
    - Better to differentiate advanced versus early fibrosis
  - Serologies impacted by inflammation
  - Indeterminate outcomes common

Lin ZH, et al *Hepatology.* 2011;53:726-736.
Vallet-Pichard A, et al. *Hepatology.* 2007;46:32-36.
Myers RP, et al. *Dig Dis Sci.* 2003;48;146-153.
Friedrich-Rust M, et al. *Z Gastroenterol.* 2013 Jan;51:43-54

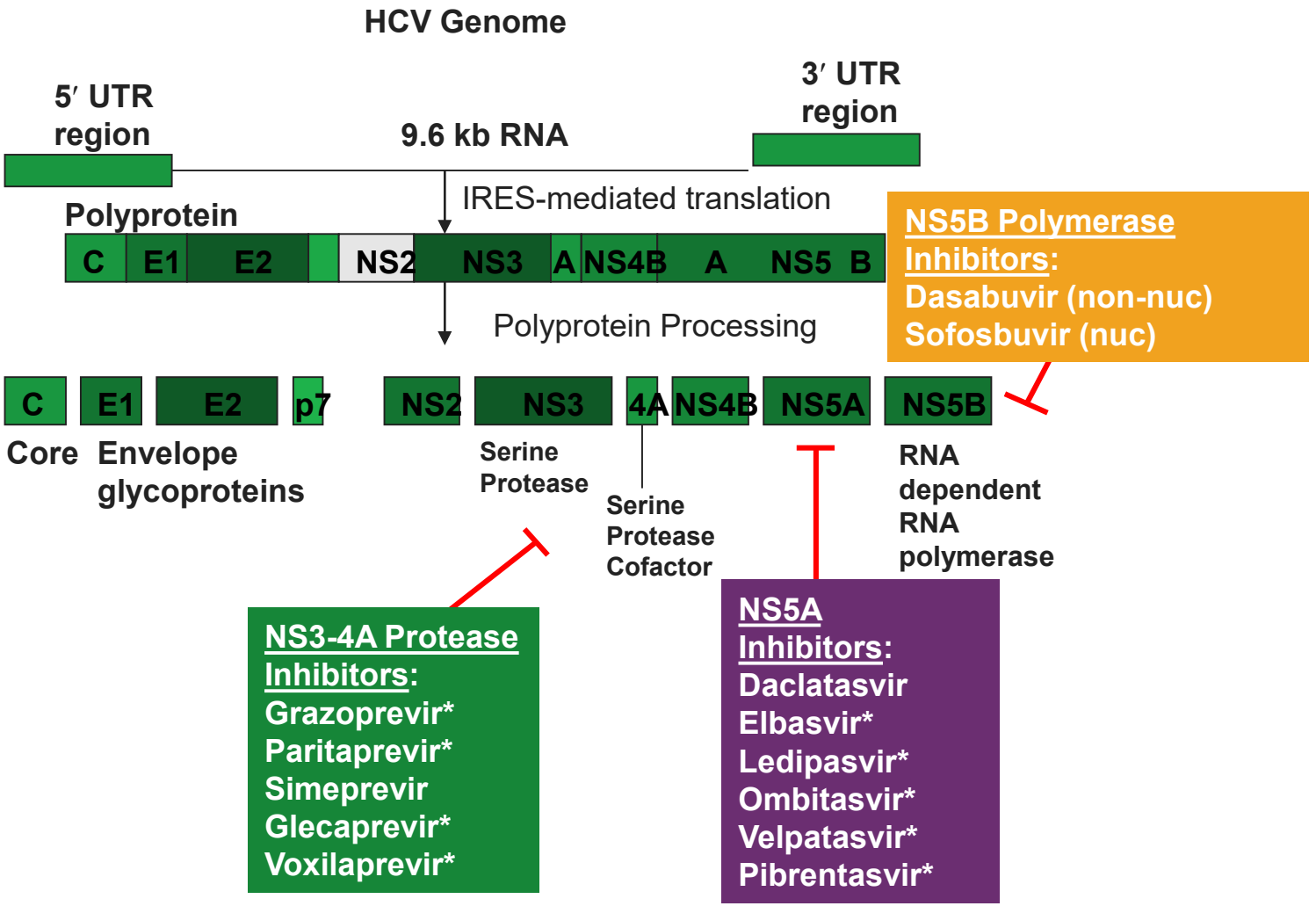
Radiographic Assessments Newer Methods

- Ultrasound, CT, MRI
  - Conventional studies are unhelpful in assessment of fibrosis unless patient has decompensated cirrhosis
- Transient elastography
  - Methodology
    - Ultrasonic transducer sends a vibration wave into the liver
    - Elastic shear wave propagates through the liver
    - Velocity of wave correlates with tissue stiffness
- Test characteristics
  - Mean AUROC for the diagnosis of:
    - Severe fibrosis: 0.89 (95% CI, 0.88-0.91)
    - Cirrhosis: 0.94 (95% CI, 0.93-0.95)

Friedrich-Rust M, et al. *Z Gastroenterol*. 2013 Jan;51:43-54.

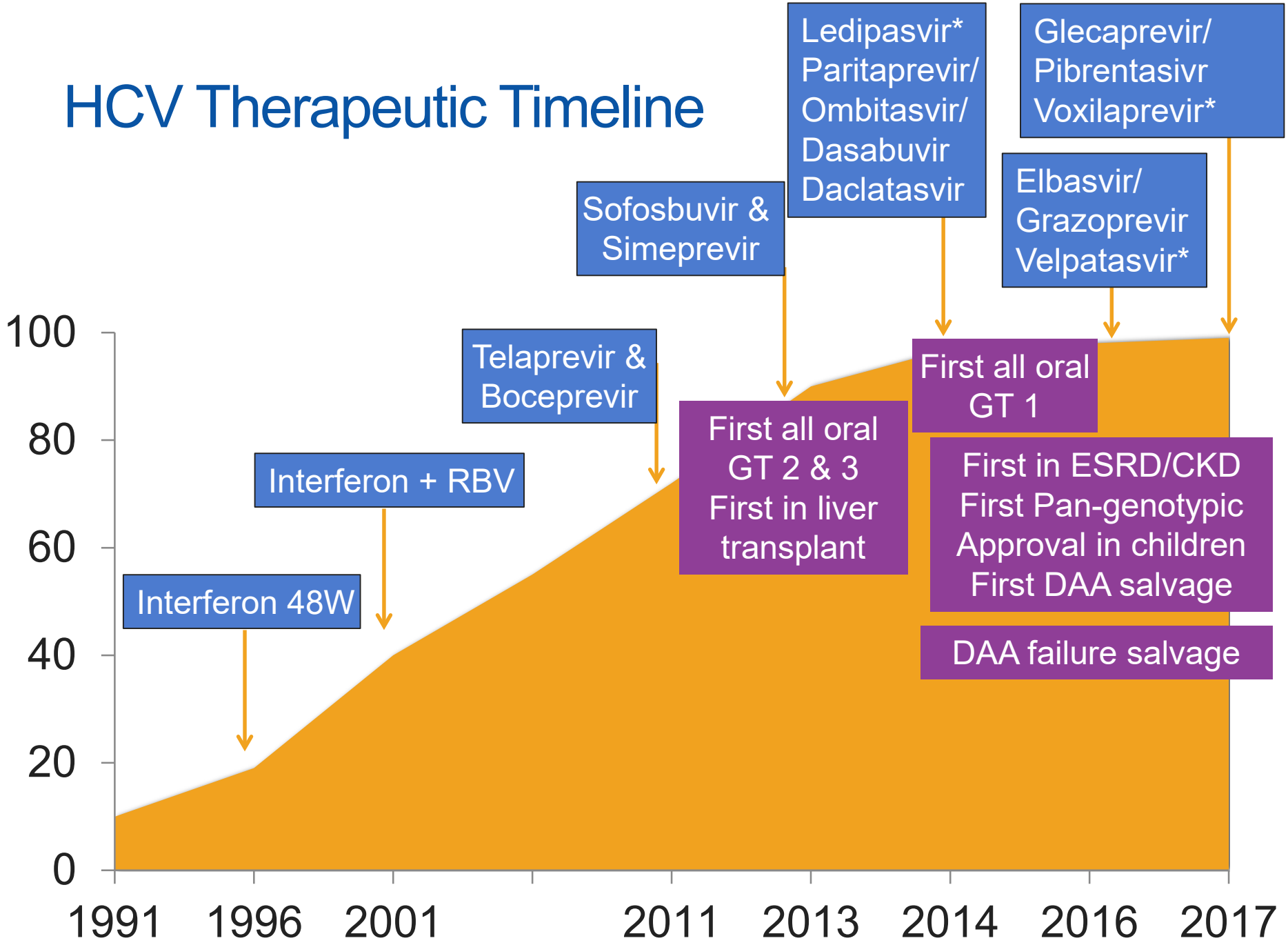
Hepatitis C Virus Drug Targets and Treatments

Hepatitis C Virus

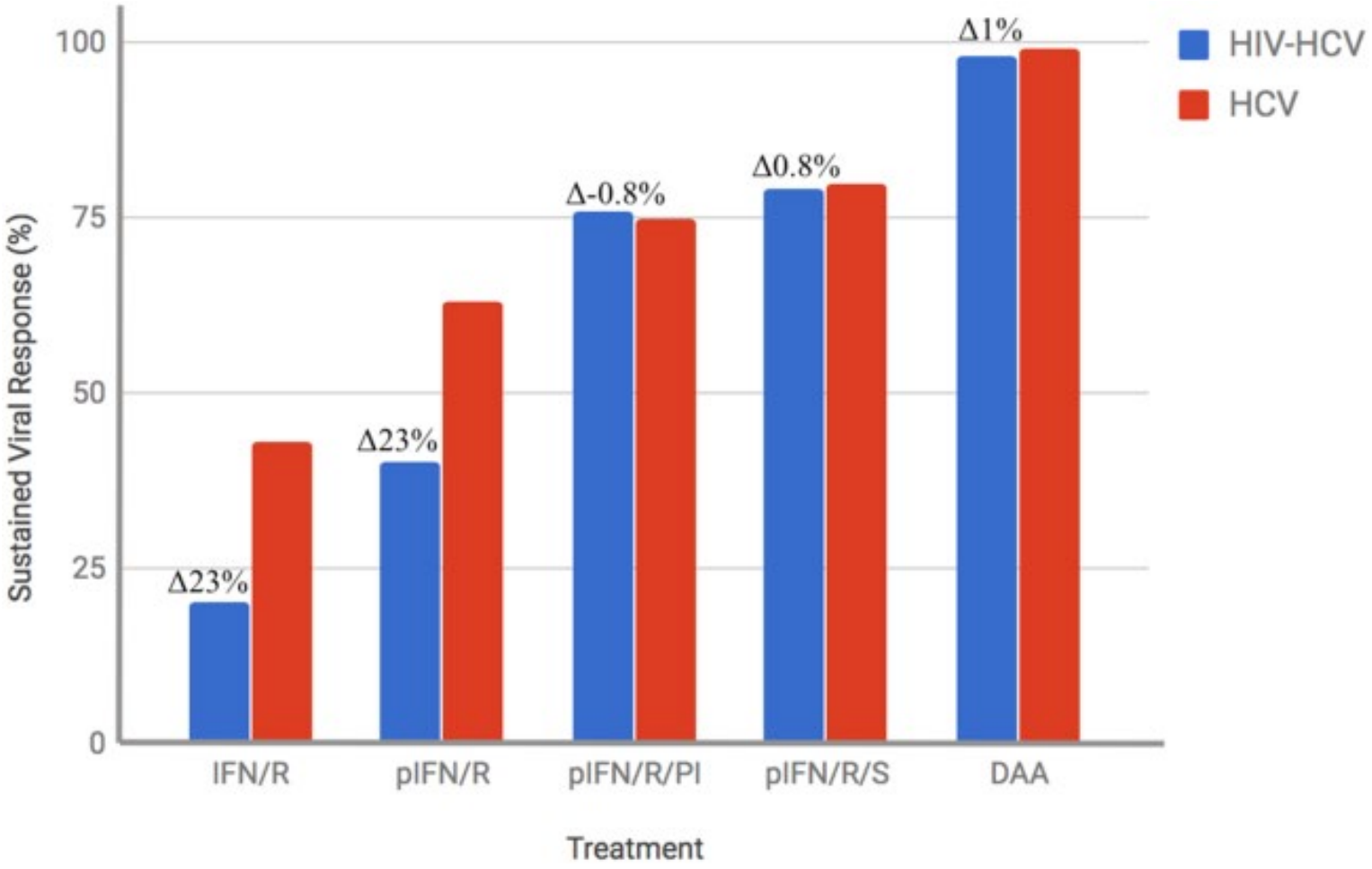


Adapted from Naggie et al. J Antimicrob Chemother 2010

HCV Therapeutic Timeline



Closing the Gap in HIV



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Hepatology, Volume: 67, Issue: 3, Pages: 847-857, First published: 06 November 2017, DOI (10.1002/hep.29642)

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C

IDSA
Infectious Diseases Society of America

Home | Test, Evaluate, Monitor | Treatment-naive | Treatment-experienced | Unique Populations | About

Start Here: Choose a patient profile from the menu above. ⤴ ×

Welcome to the New HCVGuidelines.org

The AASLD and IDSA in partnership with the panel have created an updated web experience to facilitate easier and faster access to this important resource. Please select a patient profile from the menu above, click on a Guidance section below, or use the search box to begin.

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Goal of Treatment

- **The goal of treatment of HCV-infected persons is to reduce all-cause mortality and liver-related health adverse consequences, including end-stage liver disease and hepatocellular carcinoma, by the achievement of virologic cure as evidenced by a sustained virologic response.**
  Rating: Class I, Level A

Recommendations for When and in Whom to Initiate Treatment

- **Treatment is recommended for all patients with chronic HCV infection, except those with short life expectancies that cannot be remediated by treating HCV, by transplantation, or by other directed therapy. Patients with short life expectancies owing to liver disease should be managed in consultation with an expert.**
  Rating: Class I, Level A

Recommended regimens for treatment-naïve patients with HCV genotype 1 or 4 without cirrhosis

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Regimen	Weeks	Rating
Elbasvir/grazoprevir (except GT1a with NS5A RAS)	12	I, A
Glecaprevir/pibrentasvir	8	I, A
Ledipasvir/sofosbuvir	8*-12	I, A/B
Sofosbuvir/velpatasvir	12	I, A

* Shortening to 8 weeks is allowable if Genotype 1 and baseline VL<6 million in persons without HIV or of African descent

Recommended regimens for treatment-naïve patients with HCV genotype 1 or 4 with compensated cirrhosis

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Recommendations for Testing, Managing, and Treating Hepatitis C

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Regimen	Weeks	Rating
Elbasvir/grazoprevir (except GT1a with NS5A RAS)	12	I, A
Glecaprevir/pibrentasvir	12	I, A
Ledipasvir/sofosbuvir	12	I, A
Sofosbuvir/velpatasvir	12	I,A

Recommended regimens for treatment-naïve patients with HCV genotype 2 or 3 without/with cirrhosis

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AASLD

Recommendations for Testing, Managing, and Treating Hepatitis C

IDSA

Infectious Diseases Society of America

Regimen	Weeks	Rating
Glecaprevir/pibrentasvir	**8/12**	**I, A**
Sofosbuvir/velpatasvir*	**12**	**I, A**

*for genotype 3 infection with cirrhosis, baseline NS5A RAS testing is recommended

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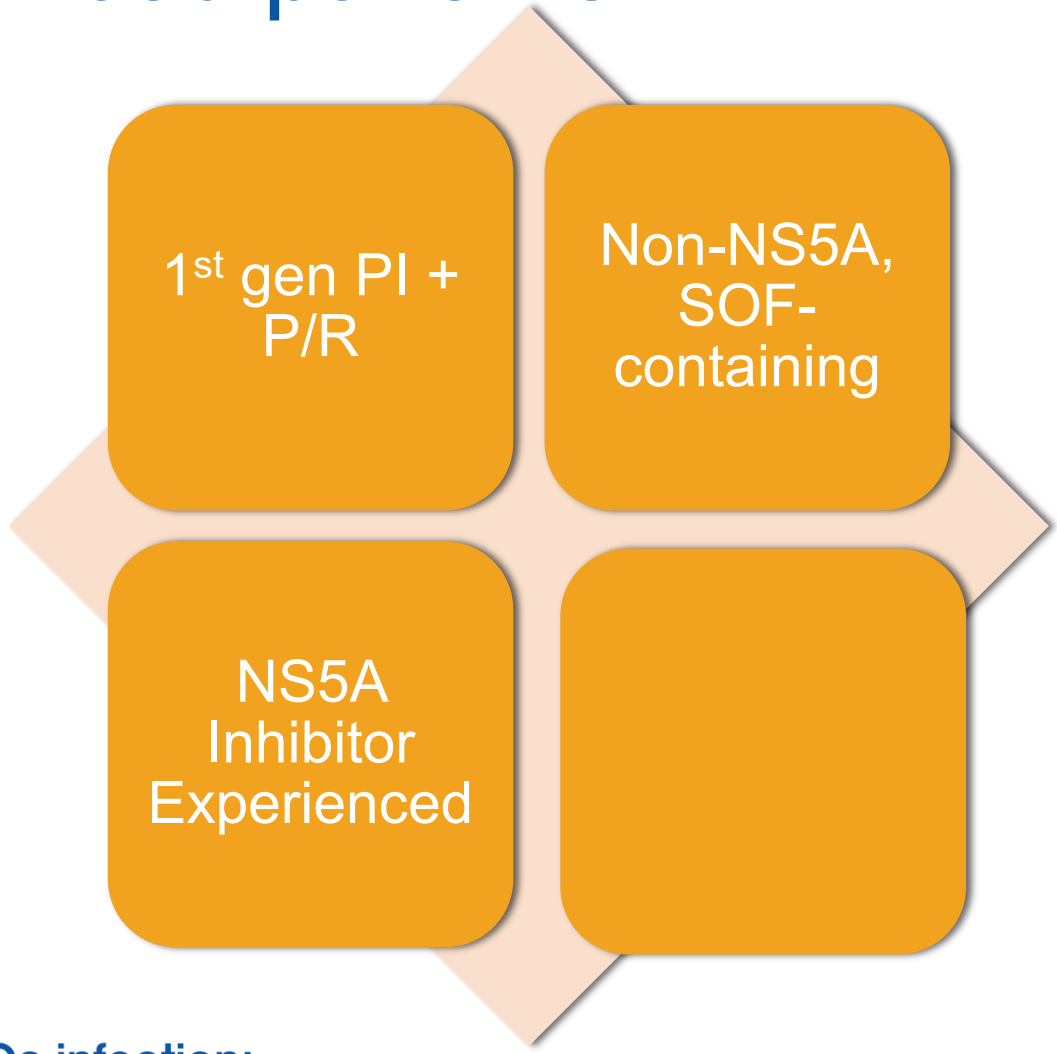
When starting therapy:

1. Genotype/subtype
2. Cirrhosis – yes/no?
3. Prior treatment experience? To DAA?
4. Is resistance testing required?

5. Other –
    1. Renal function?
    2. Liver function? -→ Calculate Child Pugh for ALL cirrhotics
    3. Drug interactions?

Approach to retreatment for DAA experienced patients



Glecaprevir (NS3)/pibrentasvir (NS5A)

- Co-formulated – 3 pills once daily
- Pangenotypic
- Next generation
  - Active vs NS3 RAS at 80, 155, 168 and NS5A RAS at 28, 30, 31, 93
- Negligible renal excretion
- Contains a protease inhibitor
- Has ? interaction with acid suppressing medications

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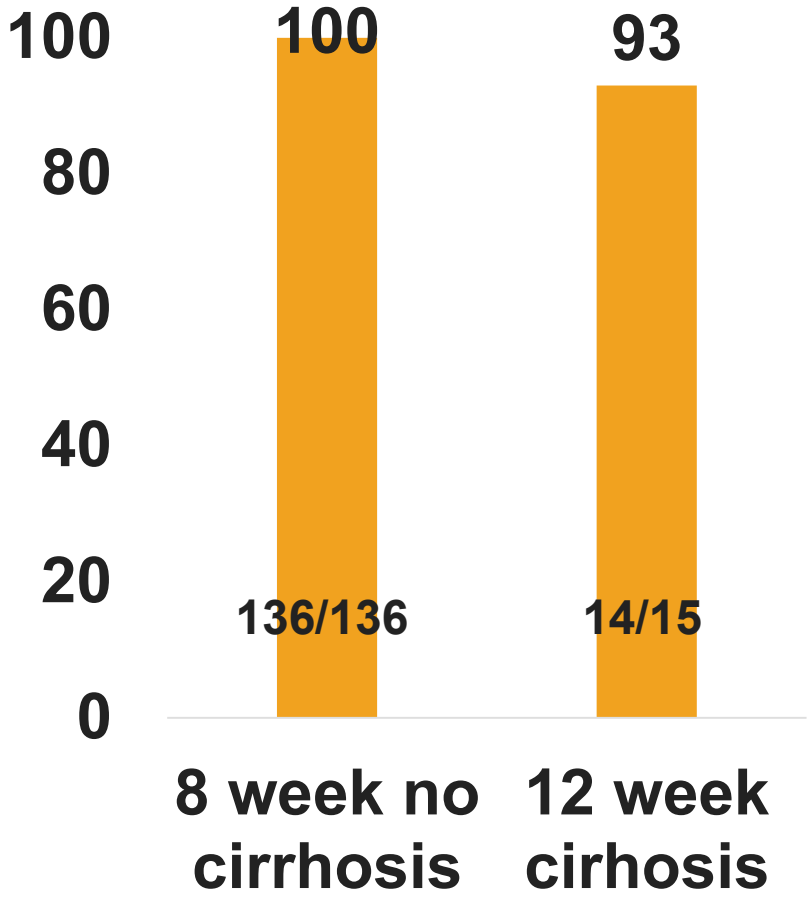
- Registration program
- 8 weeks in treatment naïve and PEG/RBV failures without cirrhosis
- 12 weeks in cirrhosis
- Renal impairment
- HIV co-infection
- Post-transplant
- Limited in DAA salvage (not in EU)
- Contraindicated in decompensated liver disease

Glecaprevir/pibrentasvir: HIV

- GT 1-6
- Primarily an 8 week study
- 12 weeks in 16 patients with cirrhosis
- TN or TE (19%) with IFN, P/R or SOF+P/R
- VBT on treatment – GT3 with cirrhosis



Rocksroh et al. EASL 2017

Sofosbuvir/velpatasvir/voxilaprevir (NS3)

- Single fixed dose combination daily pill
- Pangenotypic
- Next generation?
  - Active vs NS3 RAS at 80, 155, 168
  - and NS5A RAS at 28, Q30, 31
- Contains a protease inhibitor
- Sofosbuvir still with limited renal data
- Velpatasvir still with acid suppressing issue

Sofosbuvir/velpatasvir/voxilaprevir (NS3)

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- Pangenotypic
- Next generation?
  - Active vs NS3 RAS at 80, 155, 168
  - and NS5A RAS at 28, Q30, 31
- Contains a protease inhibitor
- Sofosbuvir still with limited renal data
- Velpatasvir still with acid suppressing issue
- Registration program
- 8 weeks in treatment naïve and PEG/RBV failures
- DAA salvage
  - Non-NS5A
  - NS5A
- No data in HIV, transplant, renal disease
- Contraindicated in decompensated liver disease

Drug interactions of DAA and ARV

	LDV/SOF	SOF/VEL	ELB/GRZ	GLE/PIB	SOF/VEL/VOX
Boosted ATZ					
Boosted DRV					?
Efavirenz					
Rilpivirine					
Etravirine					
Raltegravir					
Elvitegravir/c				?	?
Dolutegravir					
Bictegravir					
TDF					
TAF					

Other Pretreatment Assessments

HCV Pretreatment Assessment

- Active Substance Use
  - **Not a contraindication**; only if interferes with adherence
  - **NO** difference in treatment outcomes
  - Is re-infection a concern?
  - Alcohol use: educate patients on impact on HCV
  - Opportunity for medication assisted treatment (MAT) for opioid use disorder (OUD) or alcohol use disorder (AUD)

HCV Pretreatment Assessment

Barriers to adherence – assess readiness

- The purpose of the adherence assessment is to optimize support, not to deny access to treatment.
- Though HCV treatment regimens are relatively short in duration, assessing a patient's readiness for treatment and ability to adhere to a medication regimen and medical care appointments before initiating DAA therapy is essential.
- After the pre-treatment assessment and before treatment initiation, a plan can be developed with the patient to address potential barriers and/or to put support resources in place
- Recommend discussing the cost of the HCV regimen with the patient, as this can reinforce the importance of adherence and value of treatment

HCV Pretreatment Assessment

- Pregnancy Status/Contraception
  - Perform pregnancy test before starting HCV treatment
  - Before ribavirin: confirm negative pregnancy test, advise patients to use 2 BCM during and for 6 months after treatment, provide BCM counseling
  - **Contraindication**: no RBV for F/M planning conception within 6 months of last dose; including M patients with pregnant partners
  - **Contraindication:** G/P and SOF/VEL/VOX and contraceptives containing ethinyl estradio

HCV Pretreatment Assessment

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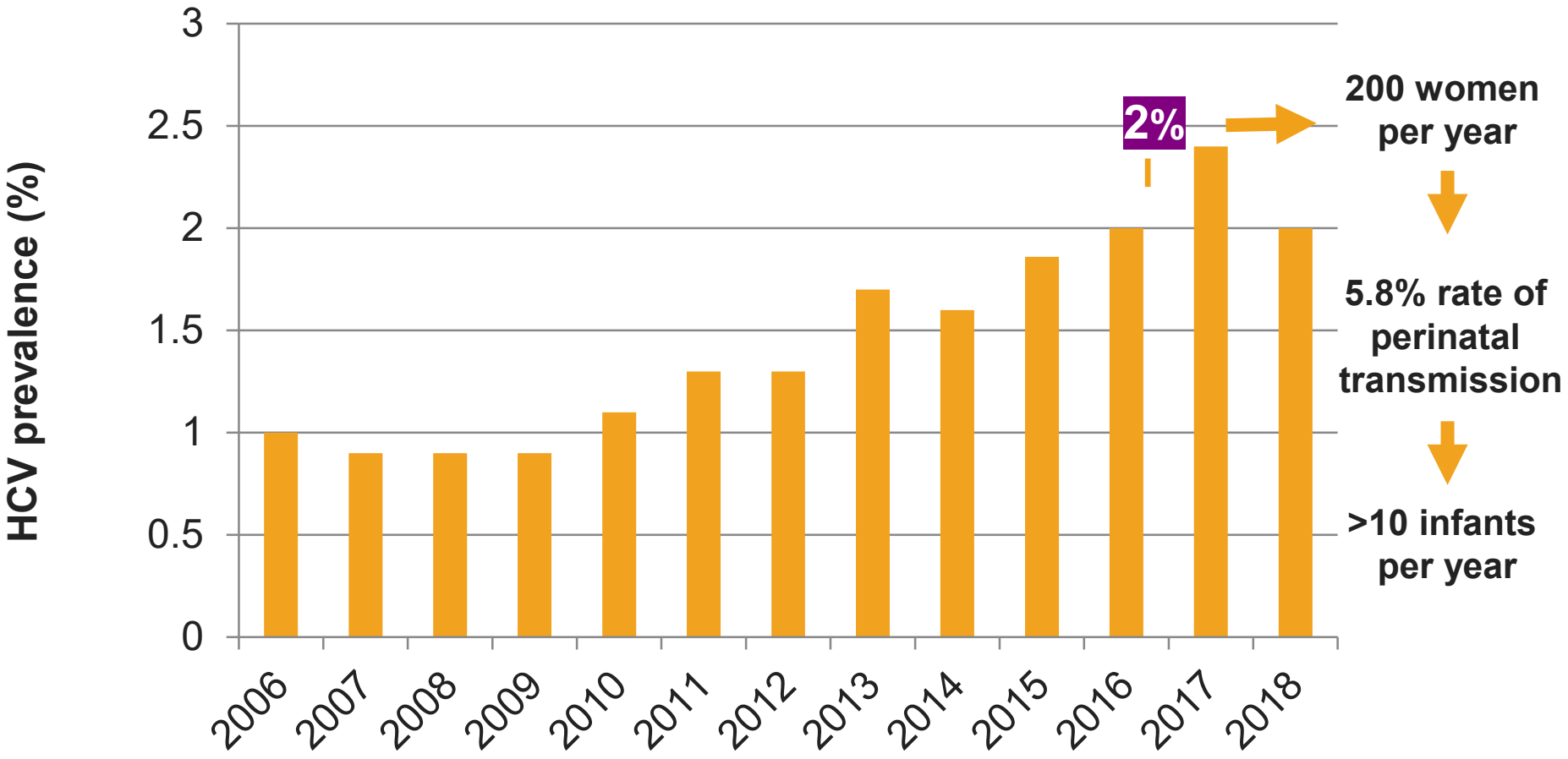
  - **Contraindication:** G/P and SOF/VEL/VOX and contraceptives containing ethinyl estradiol
  - **What if diagnosis made during pregnancy?**

? Safety in Pregnancy

DAA	Animal Toxicology Pregnancy	Animal Toxicology Breast Feeding/Lactation
Sofosbuvir/Velpatasvir ± Voxilaprevir	No observed AE Sof with increased exposures during gestation	All DAA detected in breast milk and/or pups
Ledipasvir/sofosbuvir	No observed AE	Ledipasvir detected in pups
Elbasvir/Grazoprevir	No observed AE, cross placenta	Both DAA detected in breast milk
Glecaprevir/ pibrentasvir	Gle: No data for rabbits due to low (7%) exposures; Pib no observed AE	Both DAA detected in breast mild and/or pups

Rising HCV Epidemic Among Pregnant Women Delivering at Magee-Womens Hospital in Pittsburgh, Pennsylvania



Chappell CA, et al. *Pediatrics*. 2018
Boneva L, et al. *CID*. 2014

Slide courtesy of Catherine Chappell

Study Design

12 week treatment course LDV/SOF

Enrollment 23-24 weeks' gestation

PK-visit 1 25-26 weeks' gestation

PK-visit 2 29-30 weeks' gestation

PK-visit 3 33-34 weeks' gestation

Delivery

Sustained viral response (SVR)12 visit (post-partum)

HCV viral load and adverse events

Delivery

Visit 1 (8w)

Visit 2 (6m)

Visit 3 (12m)

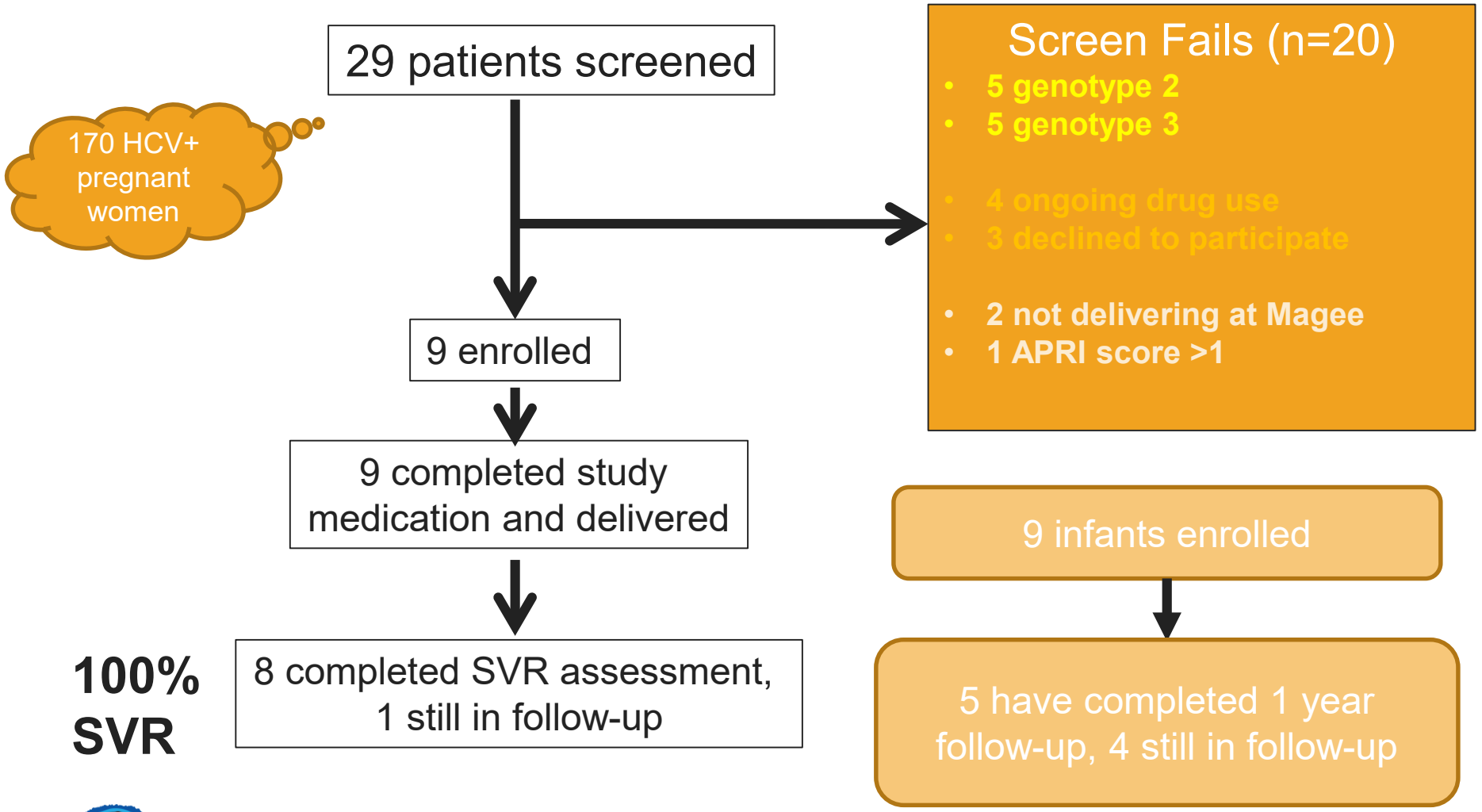
Follow-up is ongoing

HCV viral load, adverse events, physical exam, growth and neurodevelopmental assessment

HIV/HCV Co-infection: An AETC National Curriculum

Slide courtesy of Catherine Chappell, CROI 2019 Abstract #87

Recruitment: October 2016 to October 2018



Slide courtesy of Catherine Chappell, CROI 2019 Abstract #87

Take home:

- Screening for HCV in pregnant women is important for early identification and to guide testing in infant
- Emerging data of safety and efficacy, PK data pending
- Difficult conversation, larger studies are needed

What else?

HBV Reactivation

Definition:

- Loss of HBV immune control in a patient with inactive or "resolved" HBV infection

Clinically:

- Ranges from subclinical to fatal hepatitis
- Rise in HBV DNA
- ALT increase (mild to very dramatic)
- May progress to liver failure/death despite antiviral therapy

Hoofnagle JH. Hepatology. 2009;49(5 suppl):S156-S165.

Agents Reported to Cause HBV Reactivation

Risk Stratification

Host-

HBsAg+

Isolated HBcAb+

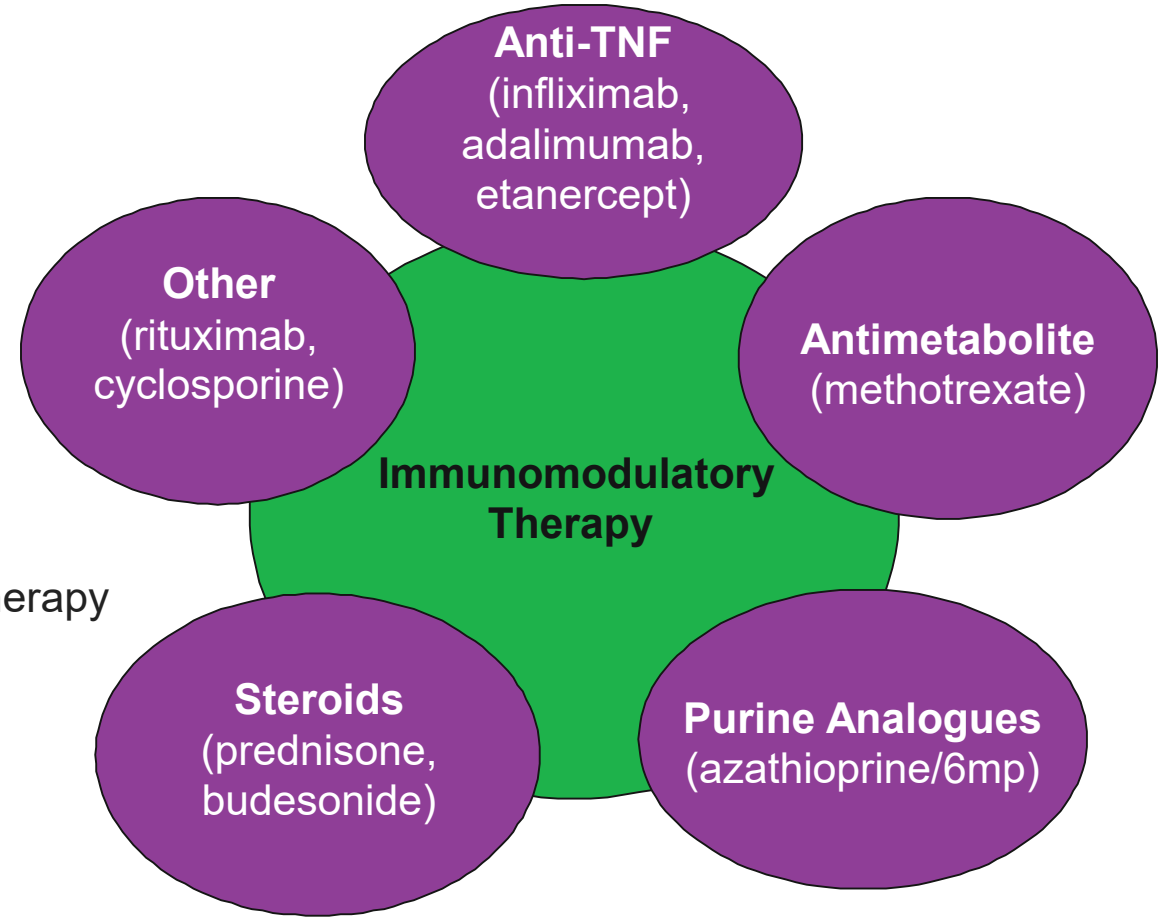
HBsAb and cAb+

Drug-

Rituximab

Cytotoxic chemotherapy

DAA



Roche B, et al. Liver Int. 2011;31(suppl 1):104-110.

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Drug Safety Communications

FDA Drug Safety Communication: FDA warns about the risk of hepatitis B reactivating in some patients treated with direct-acting antivirals for hepatitis C

Safety Announcement

[10-04-2016] The U.S. Food and Drug Administration (FDA) is warning about the risk of hepatitis B virus (HBV) becoming an active infection again in any patient who has a current or previous infection with HBV and is treated with certain direct-acting antiviral (DAA) medicines for hepatitis C virus. In a few cases, HBV reactivation in patients treated with DAA medicines resulted in serious liver problems or death.

- Between November 22, 2013 and July 18, 2016, 24 unique cases with confirmed HBV reactivation were identified, 5 more later added
- Case definition:
  - - Temporal association with HCV DAA initiation AND
  - - Evidence of increase in HBV DNA level or HBsAg seroconversion from negative to positive
- HBV reactivation usually occurred within 4-8 weeks (average-52 days) of DAA initiation
- Fatal and life-threatening events in 3 patients (deaths-2, liver transplant-1)
- A delay in identification and treatment of HBV reactivation associated with DAA therapy was noted

Bersoff-Matcha et al, Annals Int Med 2017

What do the guidelines say?

- **All patients initiating HCV DAA therapy should be assessed for HBV coinfection with HBsAg, anti-HBs, and anti-HBc.** Rating: Class IIa, Level B
- **For HBsAg+ patients who are not already on HBV suppressive therapy:**
  - **Start on NA therapy if criteria met per GL**
  - **monitoring of HBV DNA levels during and immediately after DAA therapy for HCV is recommended and antiviral treatment for HBV should be given if HBV DNA changes >10 fold from BL or >10,000 if previously <LLOQ.** Rating: Class IIa, Level B
  - **Start on NA therapy for prophylaxis for those with low level DNA <1000 or <LLOQ, continue for 12 weeks**

Take home:

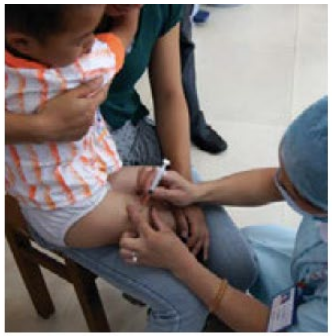
- HBVr does occur in setting of DAA therapy, although unclear it is more common
- HBVr is rare in isolated HBcAb and further testing not recommended unless ALT increase
- Prophylaxis is recommended by EASL while AASLD/IDSA provides as option vs monitoring (?risk of withdrawal of prophylaxis?)

Management Post-SVR

- When do you stop testing for HCV RNA?
- Do liver enzymes (AST,ALT) normalize? (what is normal?)
- Did patient have steatosis on imaging?
- Does patient drink ETOH?
- Did patient have severe fibrosis on pre-treatment assessment?
- HCC screening, CP and MELD monitoring, ?EGD
- Is patient at risk of re-exposure?

Questions

PREVENT

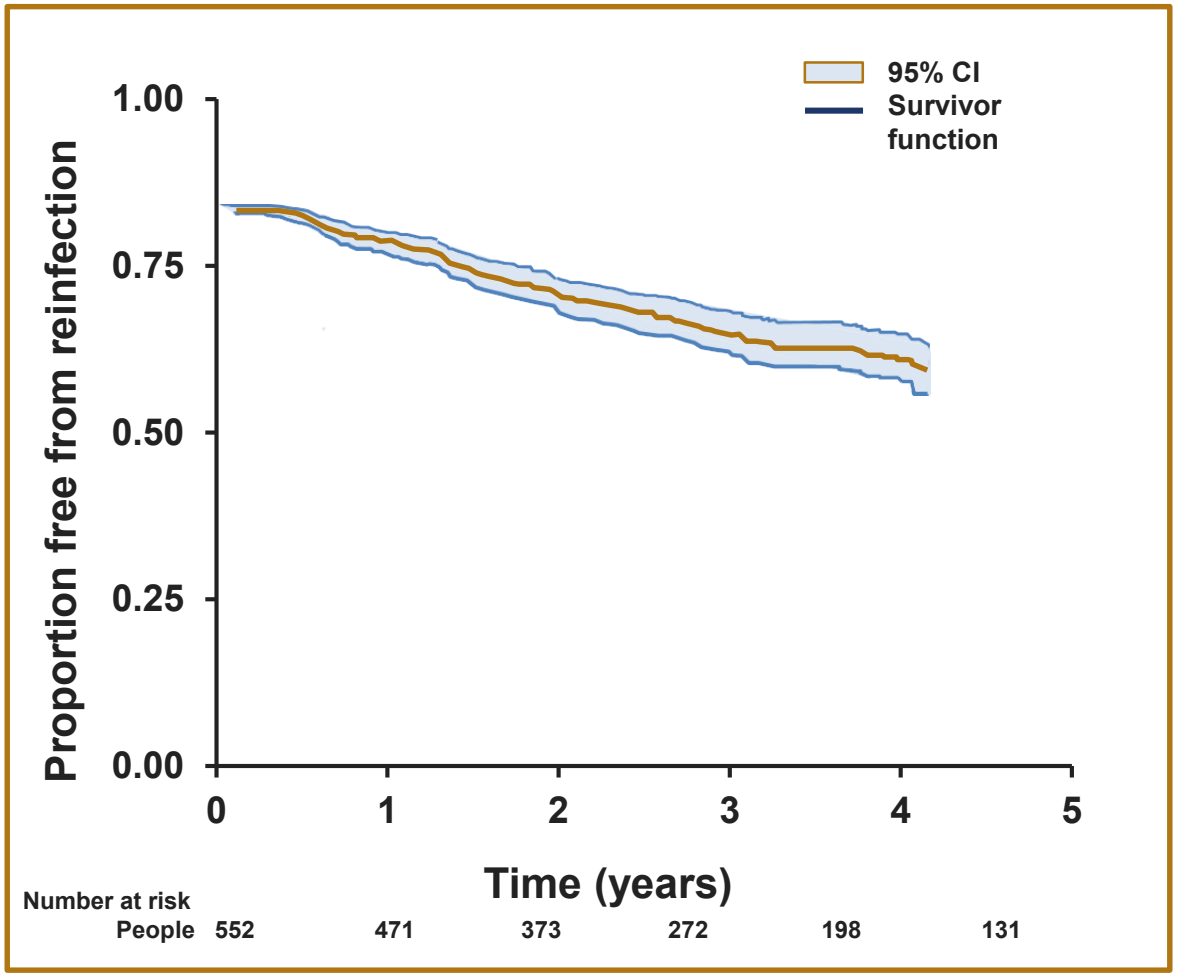


TEST

TREAT

Extras

HCV Reinfection: High in HIV-infected persons



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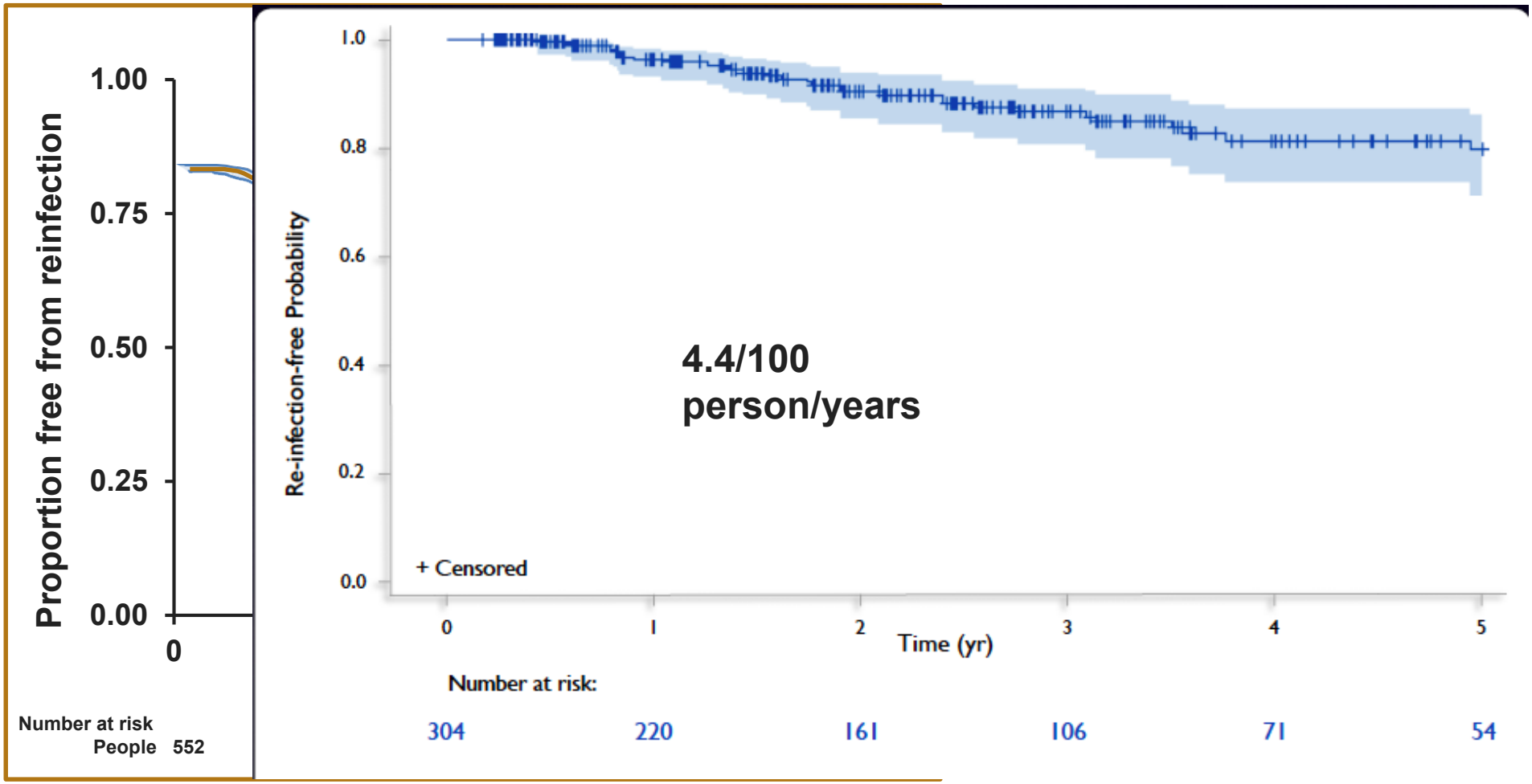
Ingiliz et al, J Hep 2016
Carollo et al. CROI 2019 Abstract #86

HCV Reinfection: High in HIV-infected persons



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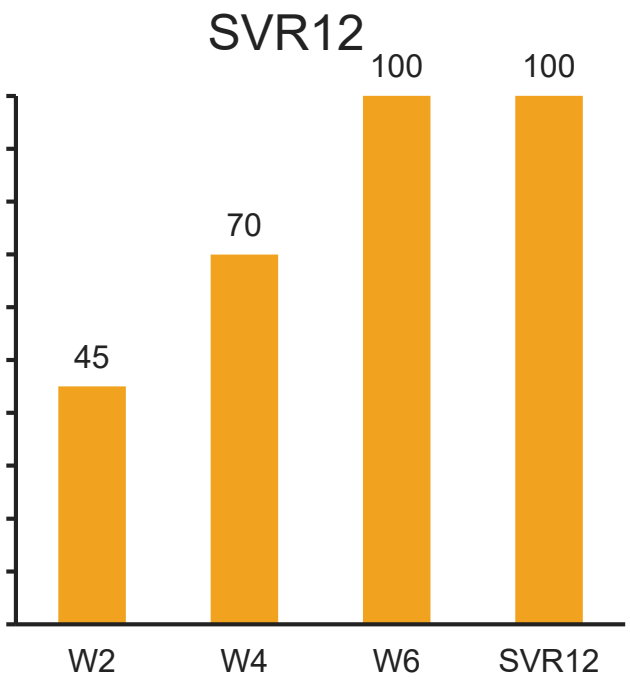
Take Home on Re-infection

- Re-infection rate in NYC (4.4/100) similar to areas of Europe
- In era of TasP, inadequate level of HCV treatment among MSM in NYC
- Gap in US in incident HCV infection rates and re-infection rates – target populations with higher prevalence and transmission riks for elimination efforts
- Need to treat early
- Prevention is essential….

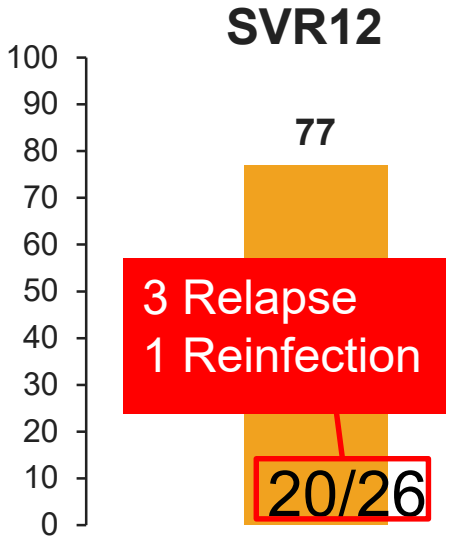
Poster 596- HPTN 078- high rates of HCV exposure in MSM without HIV (~20%), not associated with HIV Infection
Poster 598- MSM cohort recently acquired HCV, 40% without HIV infection, 67% sexual transmission

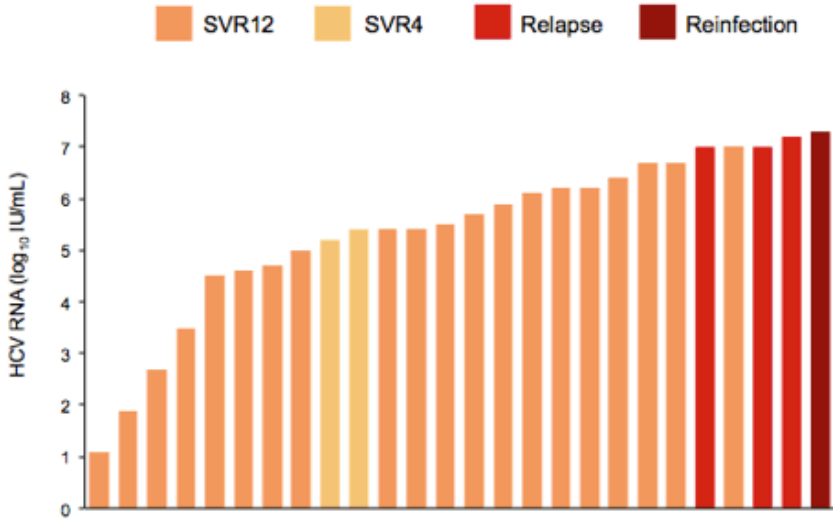
Treat early or treat as chronic?



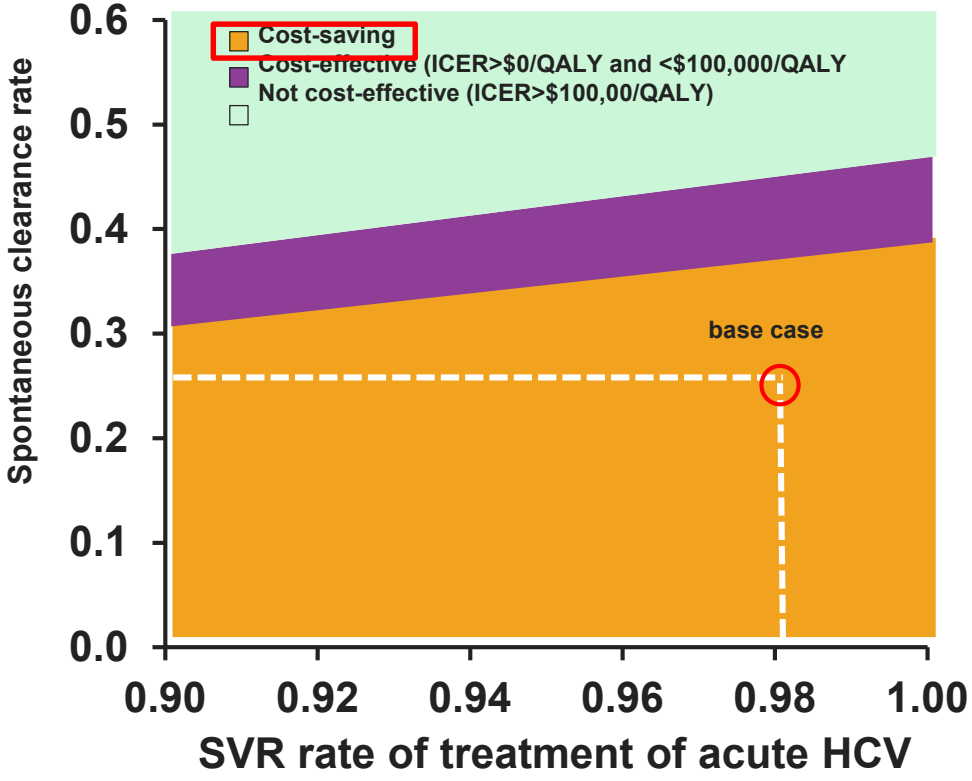
Deterding et al: N=20, not HIV infected, immediate treatment, primarily symptomatic

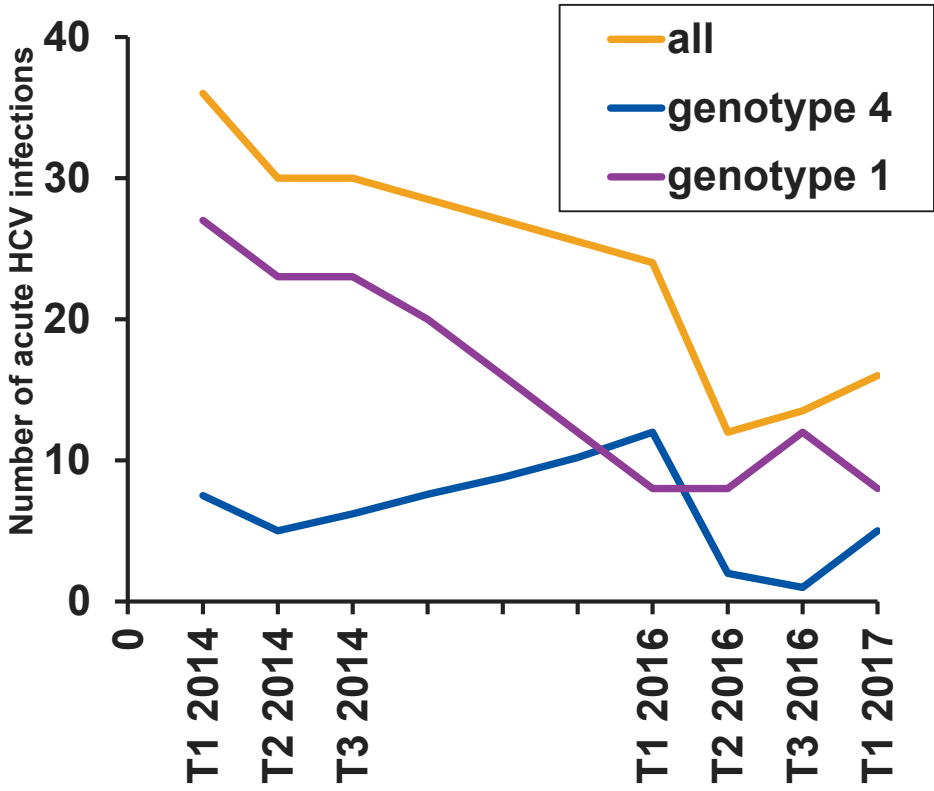
Rockstroh et al: N=26, HIV infected, later treatment, asymptomatic





HCV Infection- Treatment is Prevention

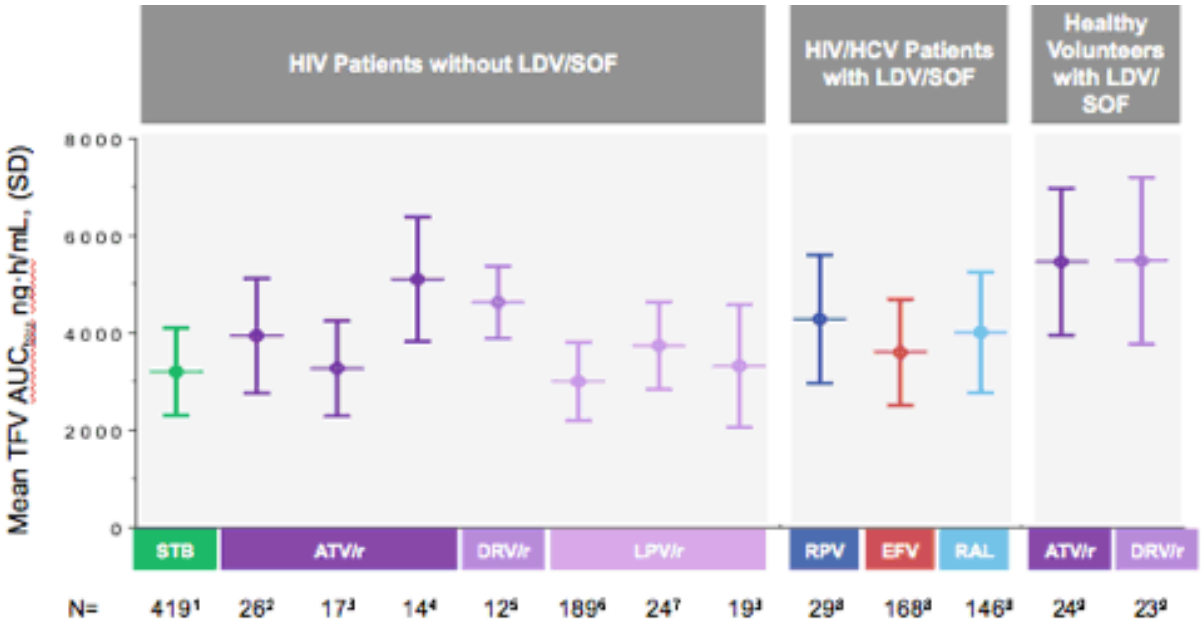




Should we treat acute hepatitis C? A decision and cost-effectiveness analysis – Bertha et al. Hepatology, 2017

Declining HCV incidence in Dutch HIV+ MSM after unrestricted access to HCV therapy – Boerekamps et al. Clin Inf Dis, 2018 in press

Ledipasvir and Tenofovir



LDV/SOF +	EFV/TDF/FTC	RPV/TDF/FTC	RAL + TDF/FTC	ATV/r + TDF/FTC	DRV/r + TDF/FTC
AUC_{tau} (ng.h/mL)	3600 (4400)	4286 (4780)	4010	5460/5740	5490/4260

German et al, Clin Pharm 2014; German et al. CROI 2015 Abstract 82; Naggie et al. NEJM 2015

Velpatasvir and Tenofovir (TDF)

LDV/SOF +	EFV/TDF/FTC	RPV/TDF/FTC	RAL + TDF/FTC	ATV/r + TDF/FTC	DRV/r + TDF/FTC
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Velpatasvir and Tenofovir (TDF)

ASTRAL 5
SOF/VEL
Unboosted
N=35

RPV, RAL

LDV/SOF +	EFV/TDF/FTC	RPV/TDF/FTC	RAL + TDF/FTC	ATV/r + TDF/FTC	DRV/r + TDF/FTC
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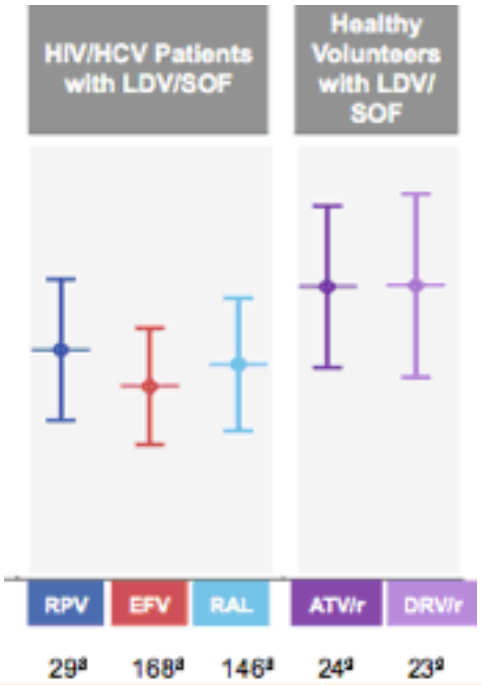

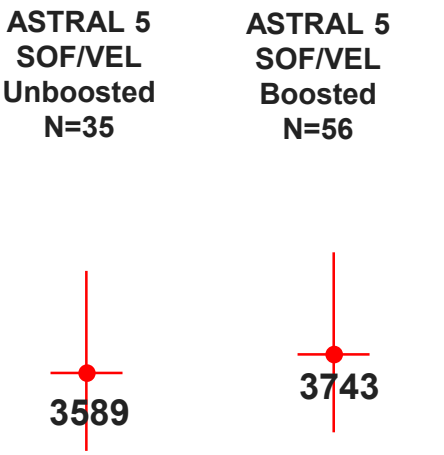

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DDI with Glecaprevir/pibrentasvir

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- Substrates of P-GP, BCRP and glecaprevir is substrate of OATP1B1/3
- Not Recommended
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  - Rifampin
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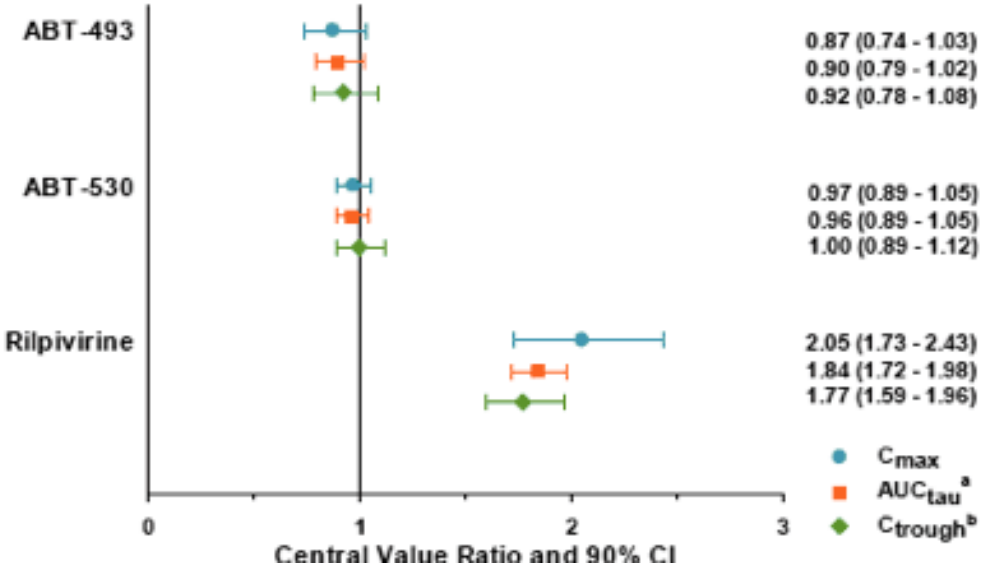
  - Statin: Atorva, Lova, Simva
  - Cyclosporine

Figure 3. Interaction between ABT-493 and ABT-530 with Rilpivirine (Central Value Ratios and 90% CIs)



Rockstroh et al. EASL 2017, Kosloski et al. CROI

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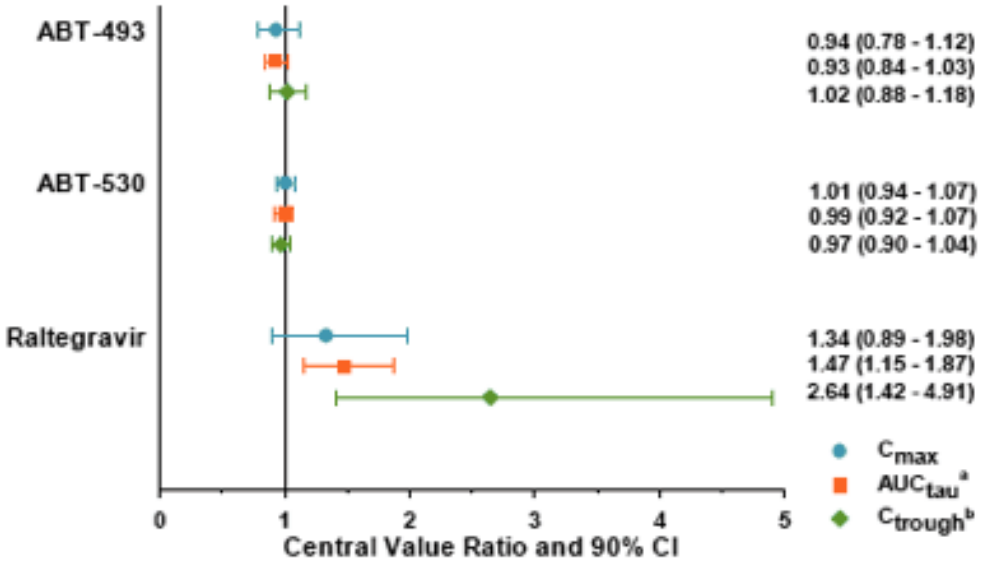
Figure 4. Interaction between ABT-493 and ABT-530 with Raltegravir (Central Value Ratios and 90% CIs)



Rockstroh et al. EASL 2017,
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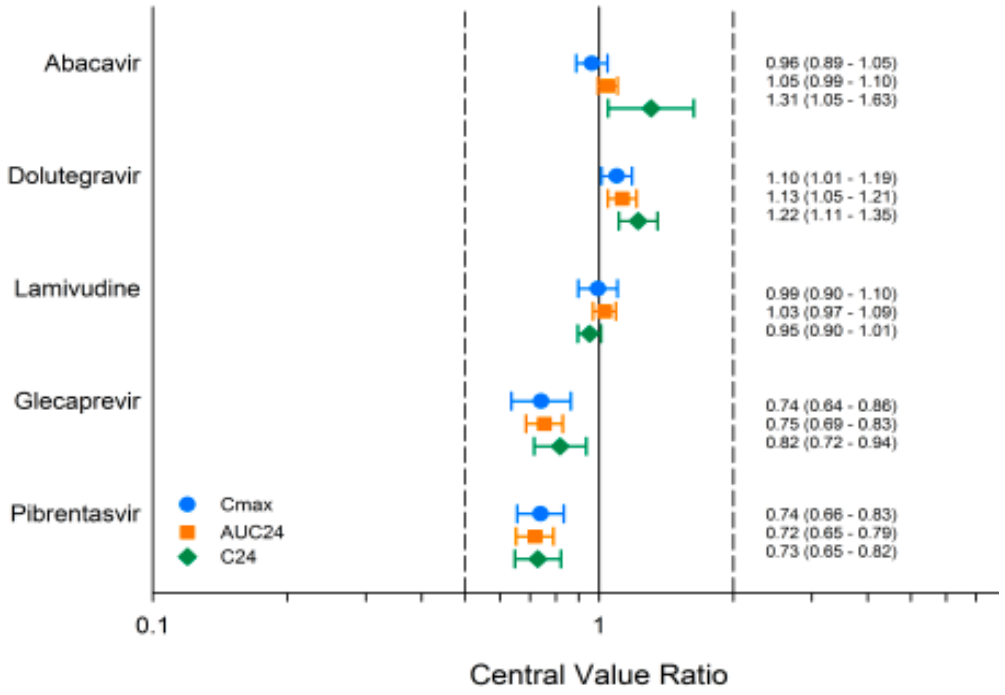

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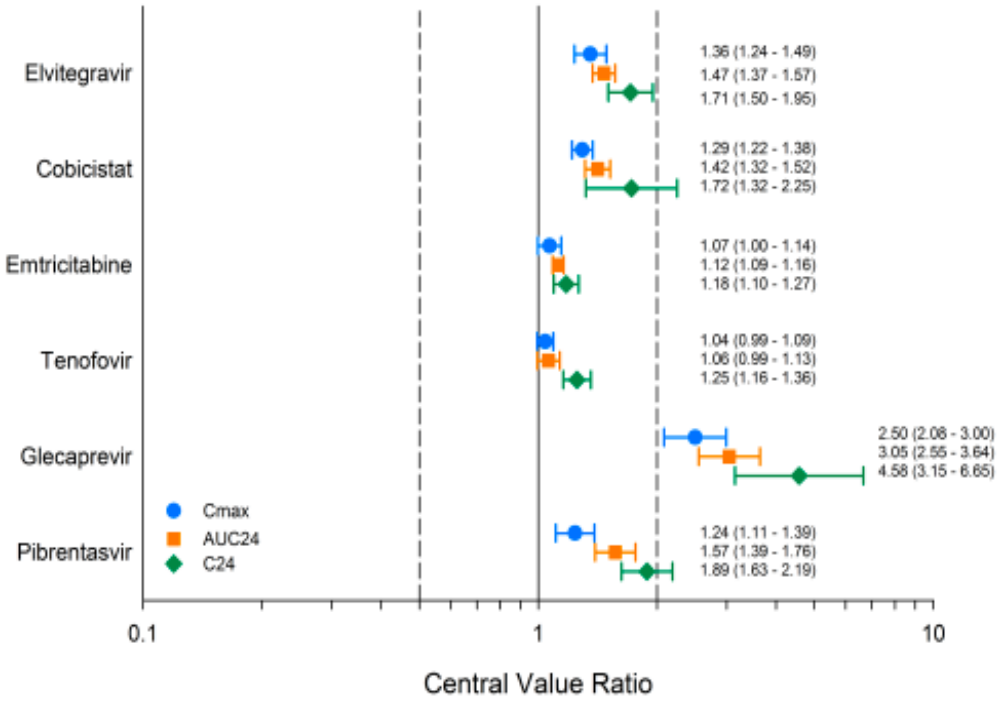

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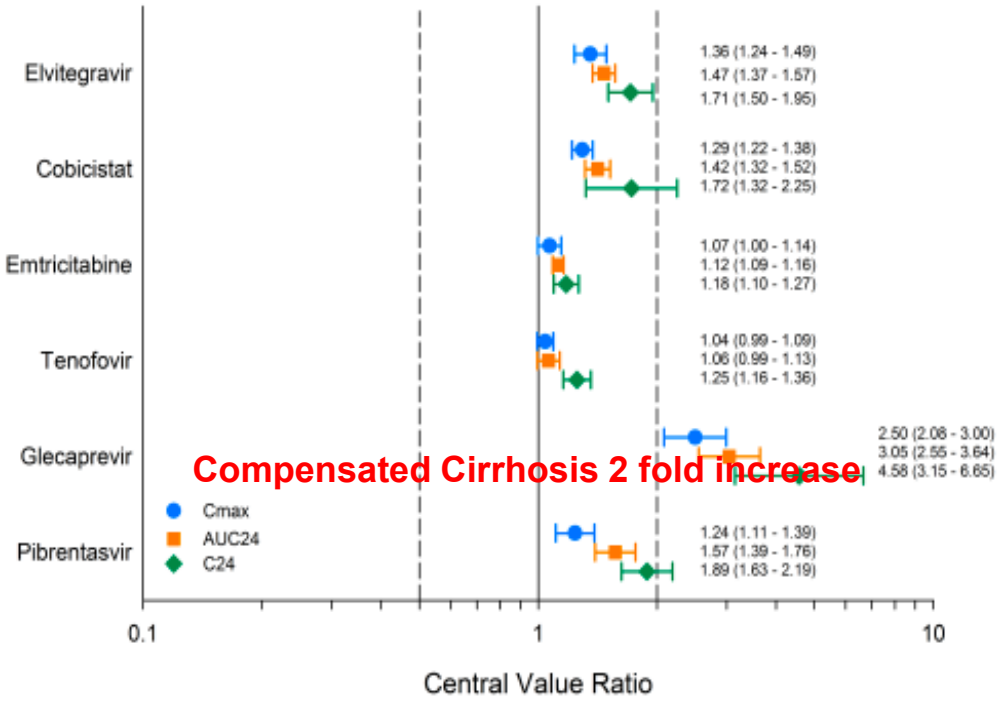

Rockstroh et al. EASL 2017,
Kosloski et al. CROI

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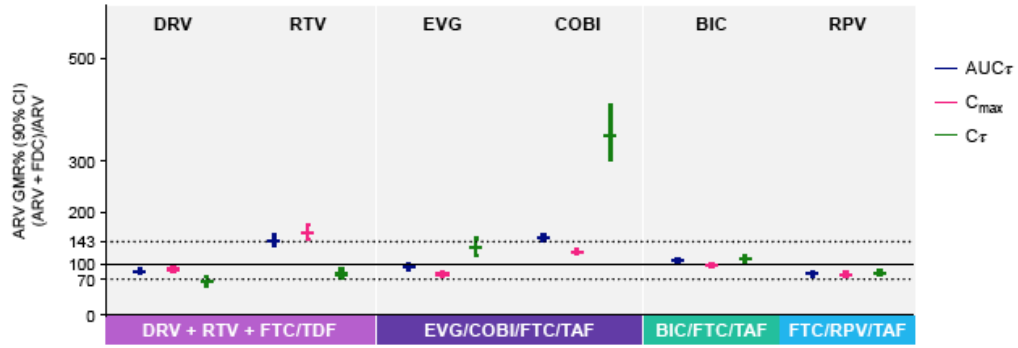
Effect of SOF/VEL/VOX on HIV ARV PK



Garrison et al, Clin Pharm AVT 2017

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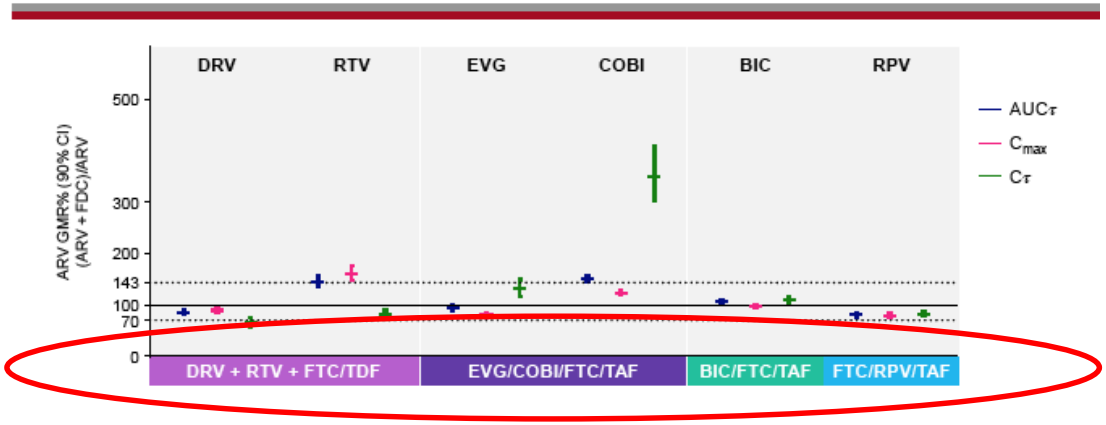

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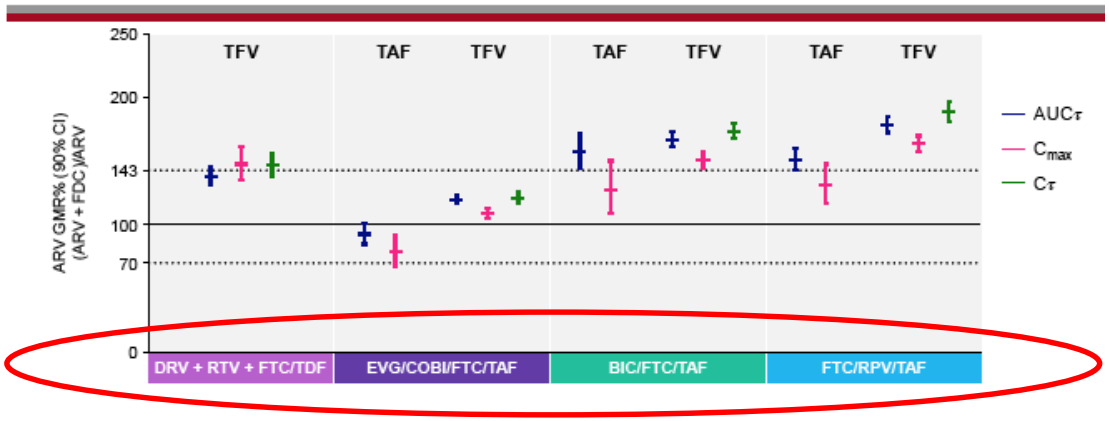

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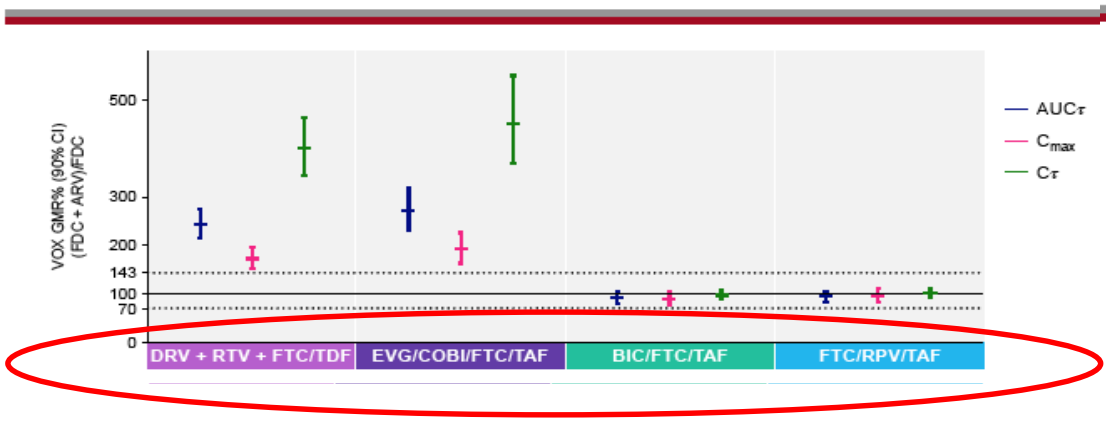
Effect of HIV ARV Regimens on VOX PK



Garrison et al, Clin Pharm AVT 2017

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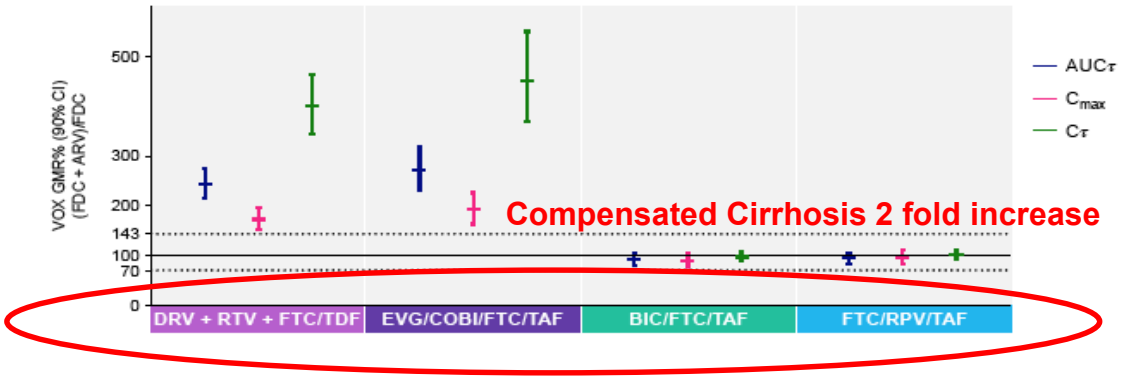

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