

Management of Hepatitis C/HIV Co- Infection: The New Era of Combination Directly Acting Antiviral Therapy

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Objectives

- **To understand the recent advances in the natural history, pathogenesis and current management strategies for Hepatitis C infection in patients with HIV**
- **To understand how Direct Acting Antiviral drugs have altered the treatment of HIV/HCV co-infected patients**

Disclosures

- **No conflict of interest to disclose**

Unlabeled/Unapproved Use

- **The following will be discussed: oral direct acting HCV drugs (not yet FDA approved for patients with HIV)**

Overview

- **The problem of hepatitis C in HIV patients**
- **Recently approved directly acting agents with data for HIV patients**
- **Future of combination antiviral therapy for HIV patients**

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Discovery of Hepatitis C

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TRANSFUSION-ASSOCIATED HEPATITIS – FEINSTONE ET AL.

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TRANSFUSION-ASSOCIATED HEPATITIS NOT DUE TO VIRAL HEPATITIS TYPE A OR B

Stephen M. Feinstone, M.D., Albert Z. Kapikian, M.D., Robert H. Purcell, M.D.,
Harvey J. Alter, M.D., and Paul V. Holland, M.D.

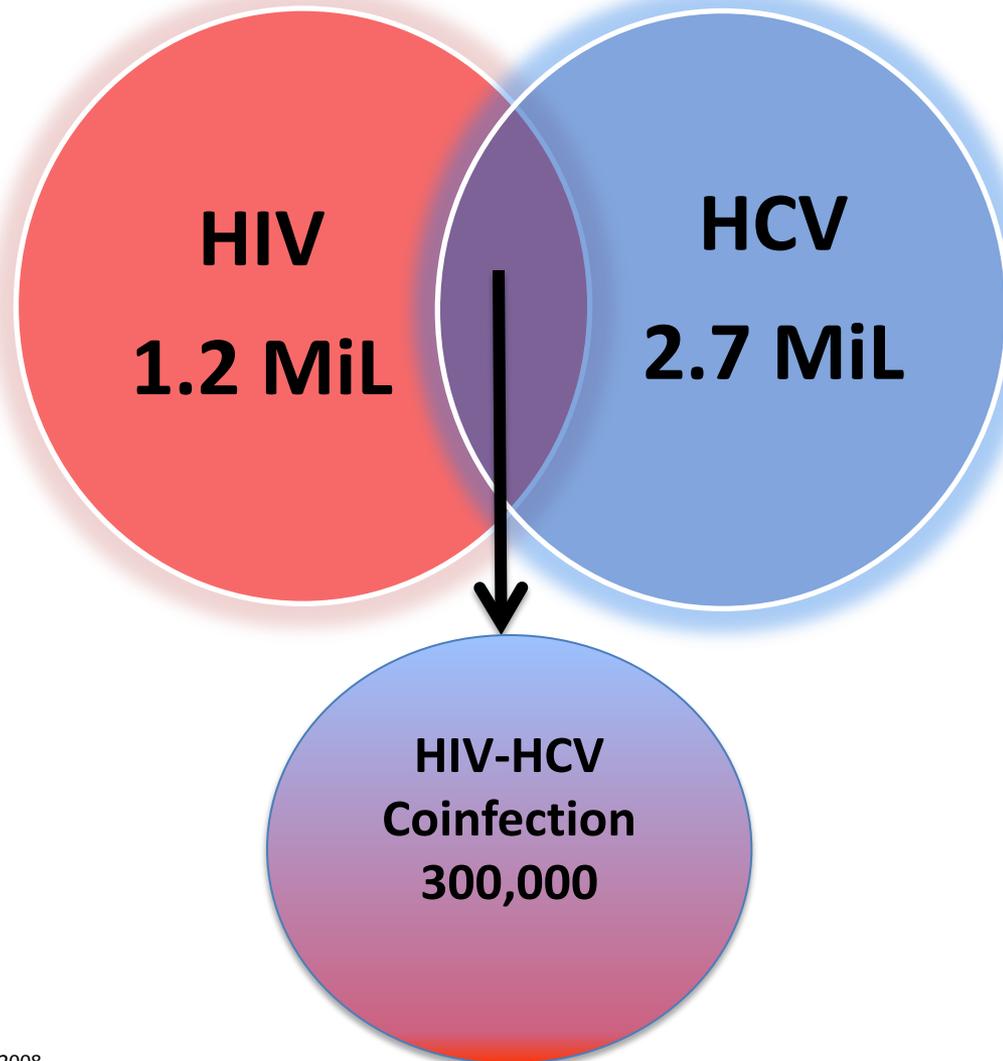
Abstract Twenty-two patients who had an episode of transfusion-associated hepatitis not positive for hepatitis B antigen were examined for development of antibody to hepatitis A and B antigens, cytomegalo-virus and Epstein-Barr virus. Antibody response to the 27-nm virus-like hepatitis A antigen was measured by immune electron microscopy. In none of the 22 patients studied did serologic evidence of infection with hepatitis A virus develop during the study period.

Nine of the 22 patients had antibody responses to cytomegalovirus, but it was difficult to relate these seroconversions to their hepatitis. In addition, all 22 patients had pre-existing antibody to the Epstein-Barr virus. It seems likely that at least a proportion of such antigen-negative transfusion-associated hepatitis is caused by other infectious agents, not yet identified. (N Engl J Med 292:767-770, 1975)

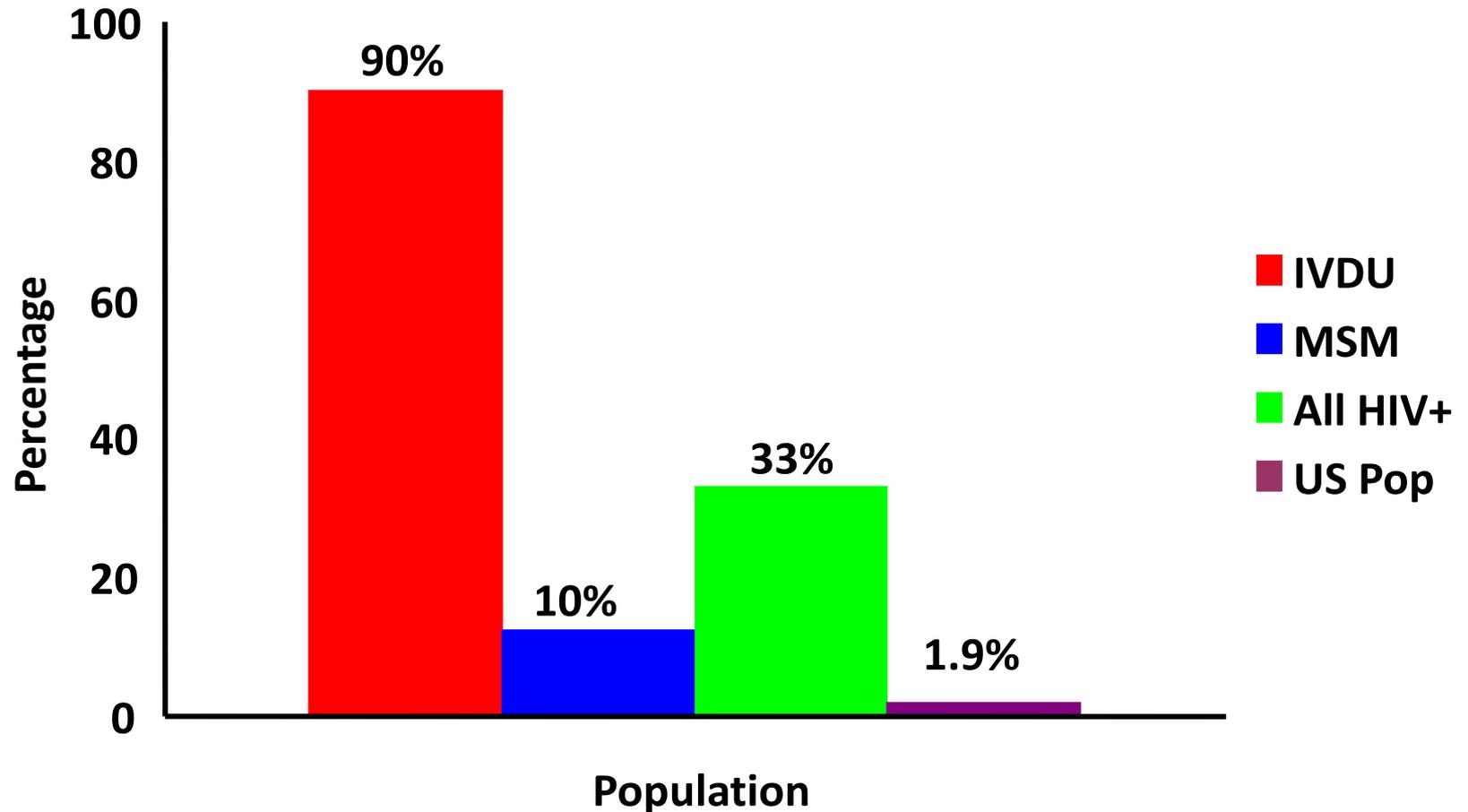
HCV Infection

- **200 million Chronic Infections Worldwide**
 - **2% of worlds population**
 - **75% of people unaware of status**

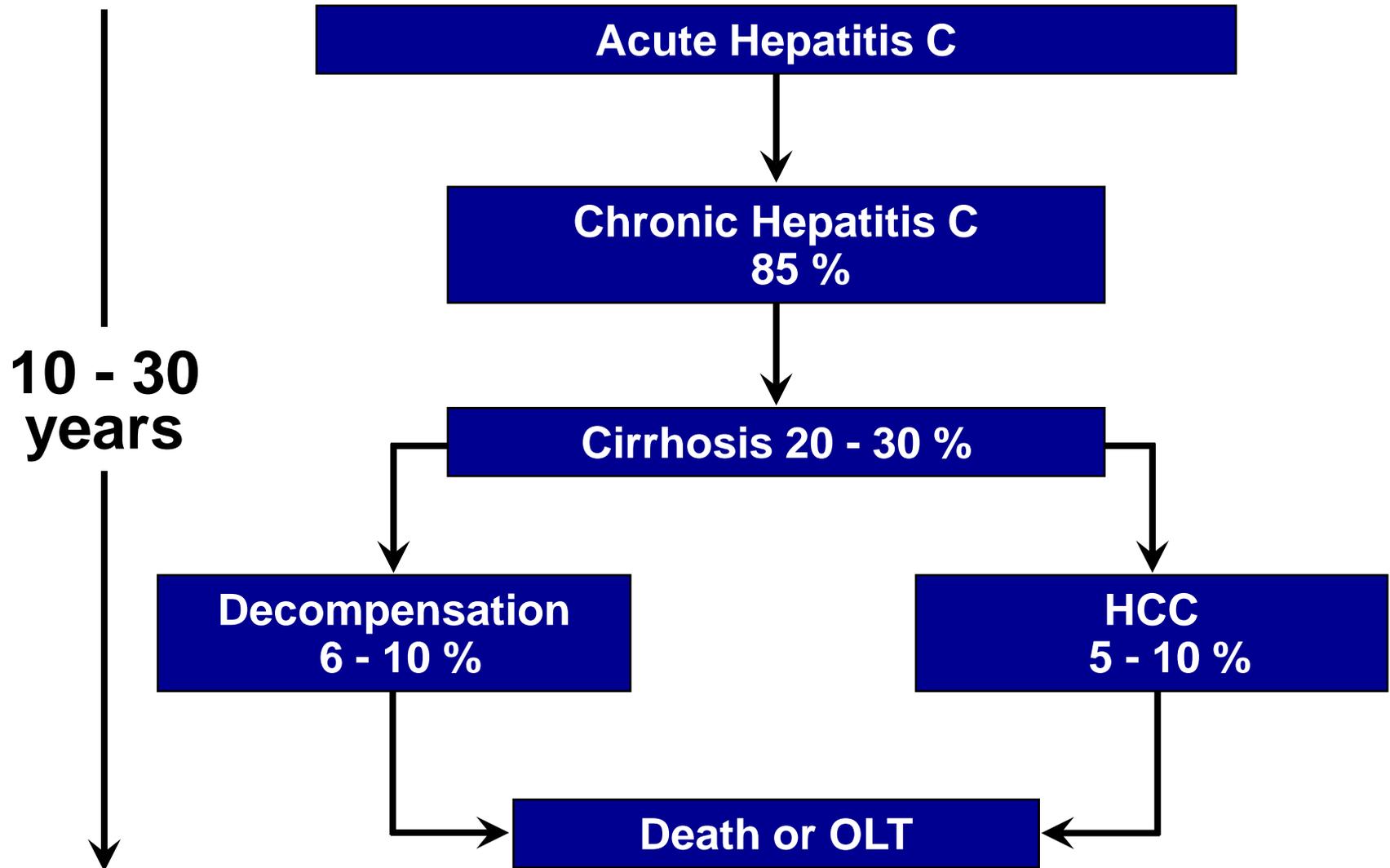
Epidemic of HIV and HCV in US



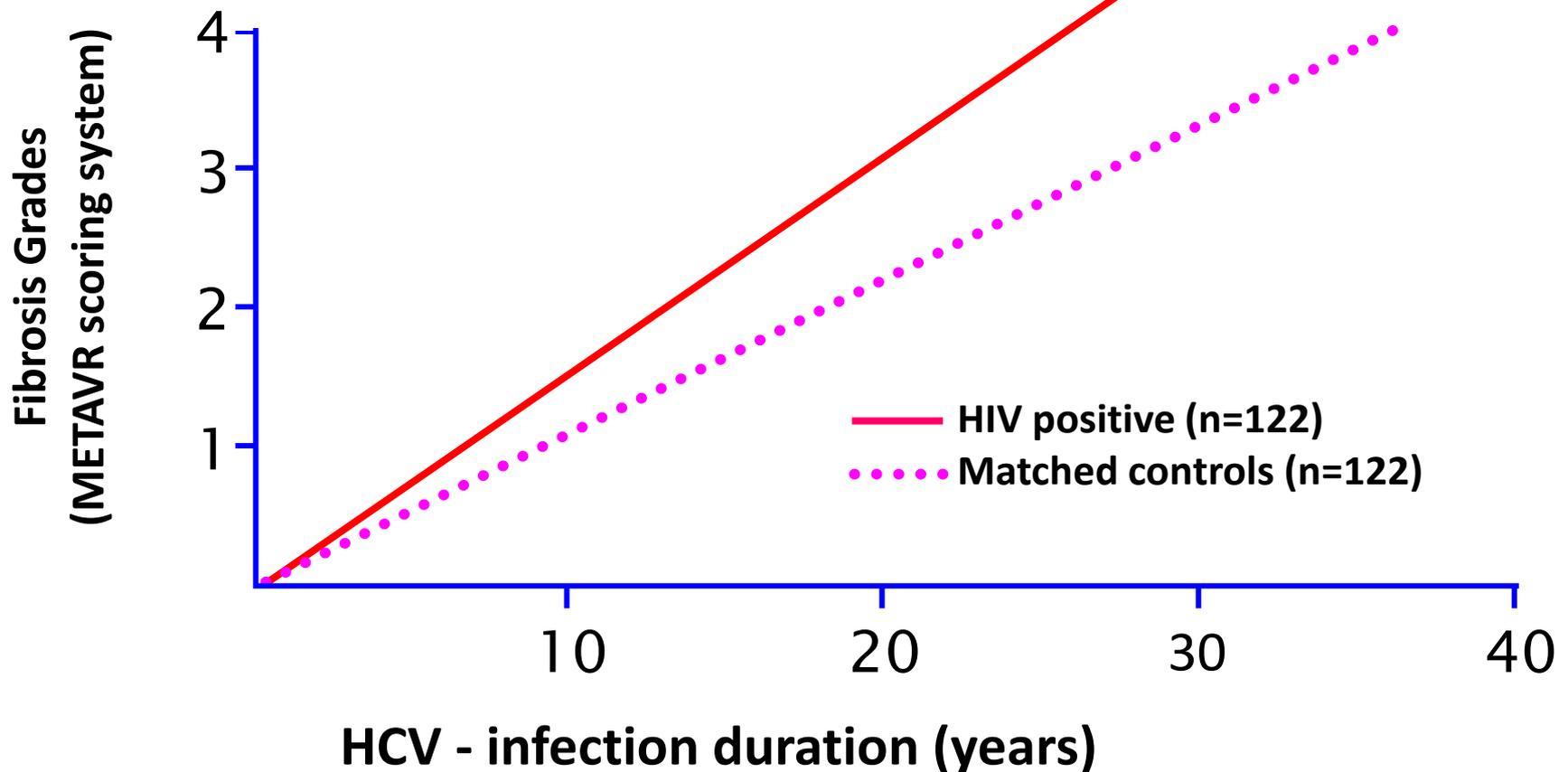
Prevalence of HCV/HIV Co-infection



Natural History of Hepatitis C



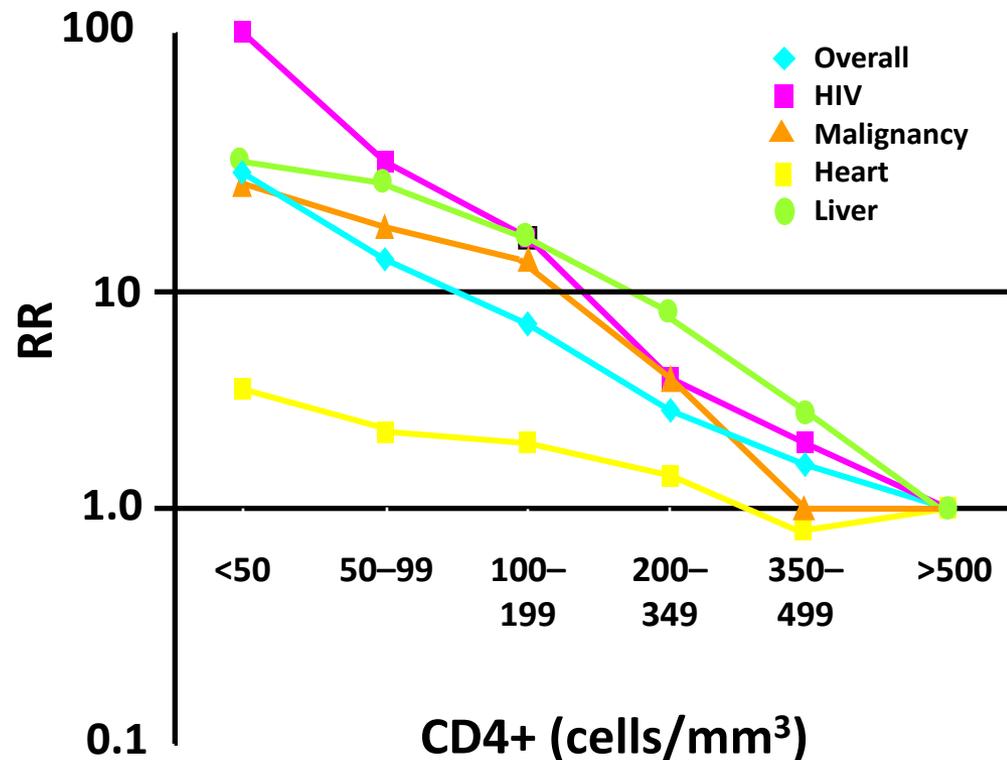
HIV Coinfection Accelerates Liver Fibrosis Progression Rate



Risk of Death in HIV-Infected (D:A:D Study)

- Cohort study of >23,000 patients in Europe, Australia, and the USA
- 1248 (5.3%) deaths 2000–2004 (1.6/100 person-years)
 - Of these, 82% on ART
- Leading causes of death
 - AIDS (30%)
 - **Liver disease (14%)**
 - Heart disease (9%)
 - Malignancy (8%)
- Predictors of liver-related death:
 - Age (RR: 1.3 per 5 years older)
 - IDU (RR: 2 vs MSM)
 - CD4+ (RR: 1.23 per halving of CD4)
 - **Anti-HCV+ (RR: 6.7)**
 - HBsAg+ (RR: 3.7)

RR of death according to immune function and specific cause

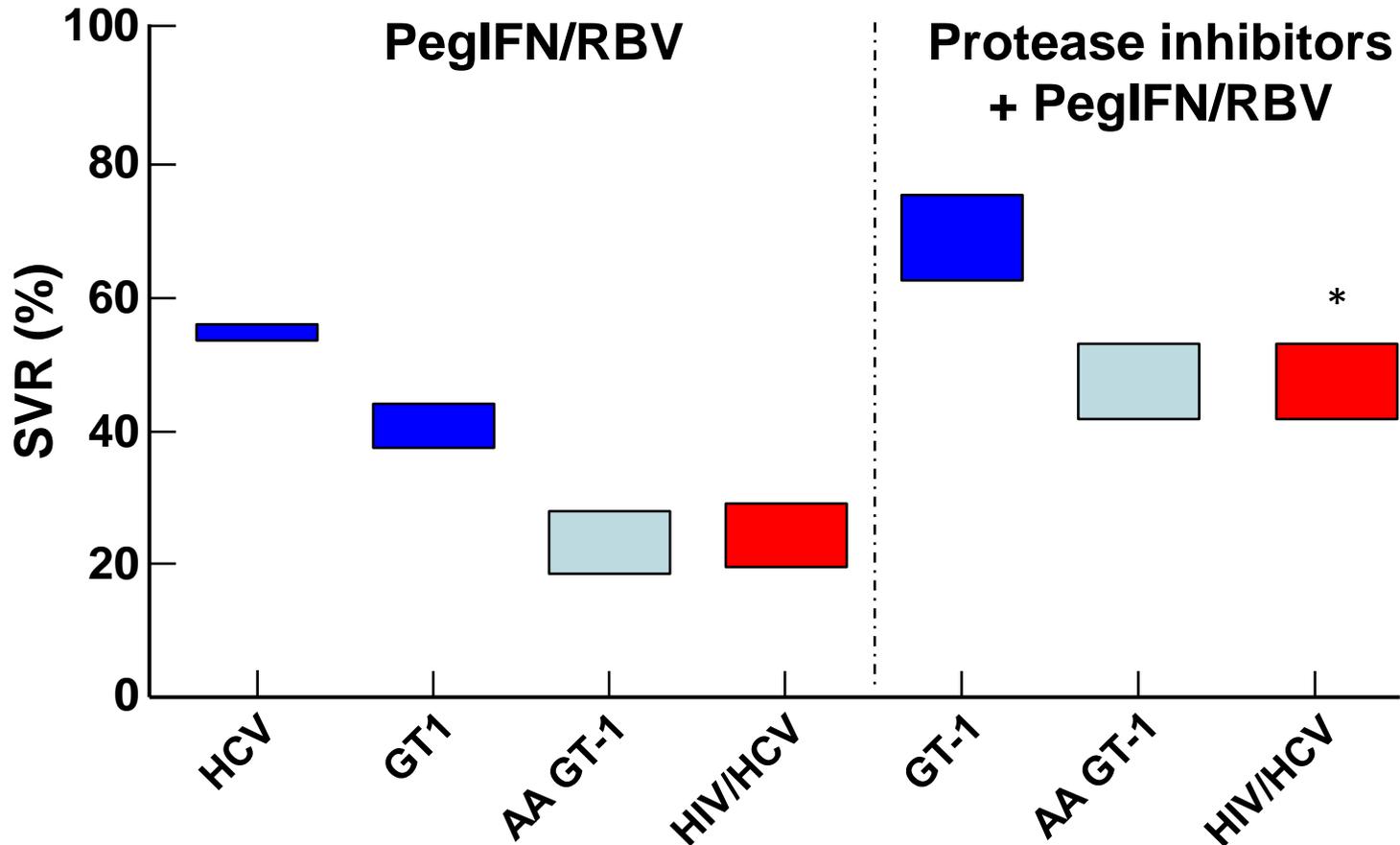


HCV can be cured unlike HIV and HBV

VIRUS	HIV	Hepatitis C	Hepatitis B
Population	1 million	5 million	2 million
Genome	RNA	RNA	DNA
Mutation Rates	Very high	Very high	High
Virions produced daily	10 ¹⁰	10 ¹²	10 ¹³
Drug Targets	Multiple	Multiple	One
Genetic archive	Yes	NO	Yes
Ability to Cure	No (Integrated viral DNA)	YES (No DNA integration)	No (cccDNA)
Current therapeutic goal	Lifelong suppression	Cure: Clearance from plasma and liver	Lifelong suppression

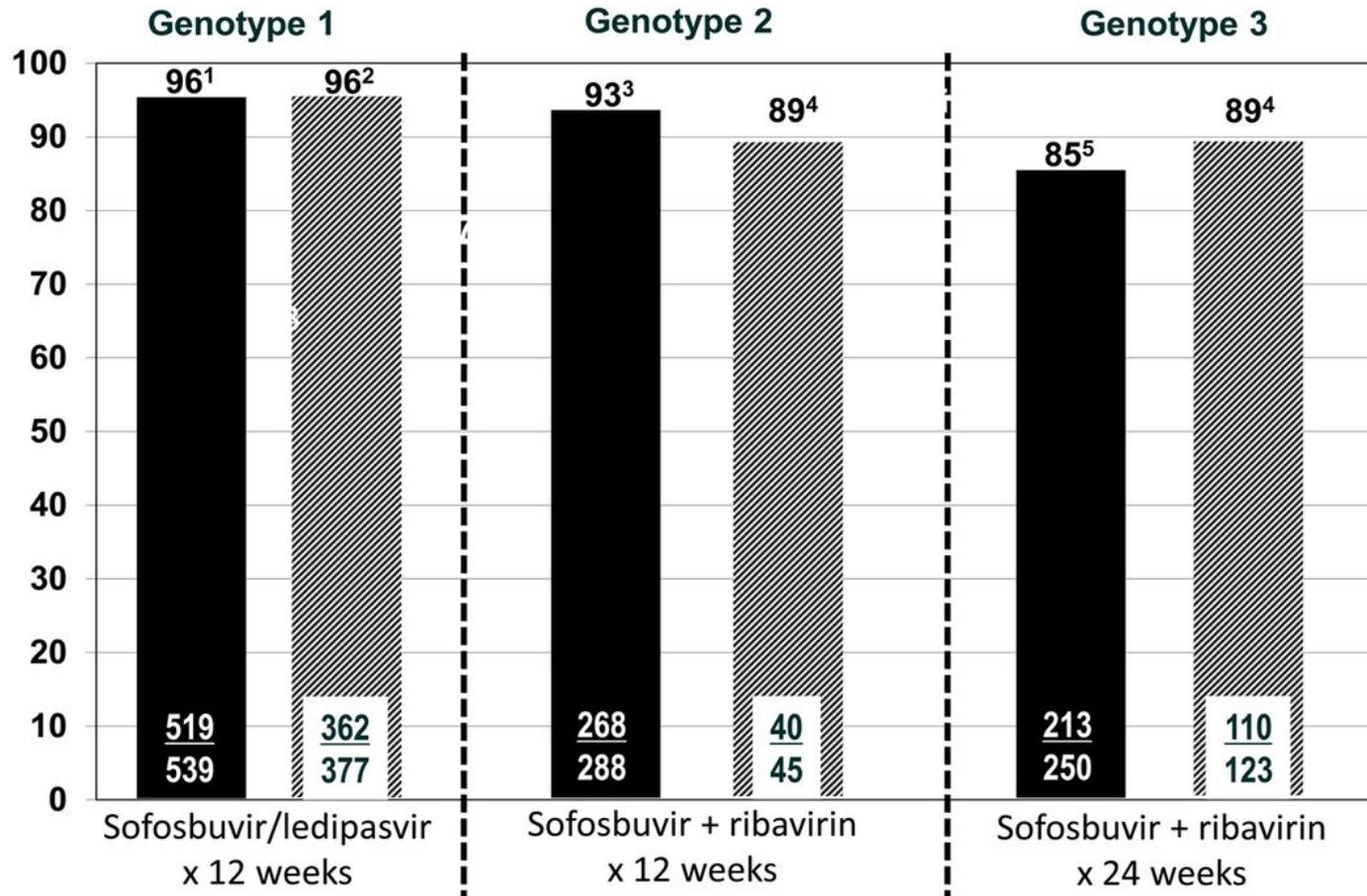
Adapted from Soriano V, JAC 2008; 62

Cure Rates for HCV



Torriani FJ, et al. *N Engl J Med.* 2004;351, Jeffers LJ, et al. *Hepatology.* 2004;39; Carrat F, et al. *JAMA.* 2004;292; Muir AJ, et al. *N Engl J Med.* 2004;350; Fried MW, et al. *N Engl J Med.* 2002;347; Manns MP, et al. *Lancet.* 2001;358. Jacobson IM, et al. *Hepatology* 2010;52; Sherman KE, et al. *Hepatology* 2010: 52, Poordad F et al. *Hepatology* 2010: 52

Cure Rates for HCV in HIV with DAAs Only Treatment Similar



HCV mono-infected
 HIV-HCV co-infected

1. ION-1, ION-2 and ION-3 [40,41,42]
2. ERADICATE and ION-4 [43,44]
3. FISSION, POSITRON, VALENCE and FUSION [32,34,35]
4. PHOTON-1 and PHOTON-2 [37,38]
5. VALENCE [35]

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- **Recently approved directly acting agents**
- **Future of combination antiviral therapy**

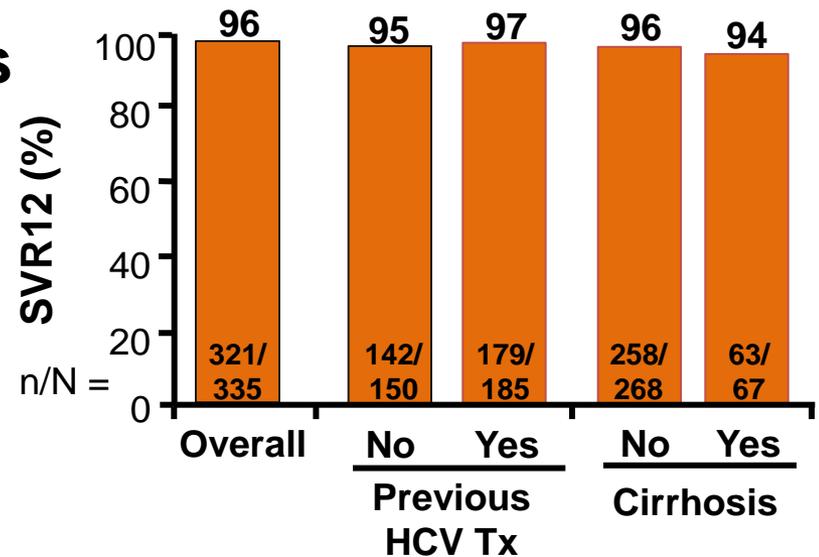


ION-4: LDV/SOF for 12 Wks in GT1/4 HCV/HIV-Coinfected Pts

- **Phase III open-label study in HIV virologically suppressed HIV/HCV coinfectd pts (N = 335)**
 - **20% with compensated cirrhosis**
 - **n = 8 with HCV GT4**
- **ART regimens**
 - **TDF/FTC/EFV (n = 160)**
 - **TDF/FTC + RAL (n = 146)**
 - **TDF/FTC/RPV (n = 29)**
- **HCV treatment experienced: 55%**
 - **Previous HCV PI therapy: 29%**

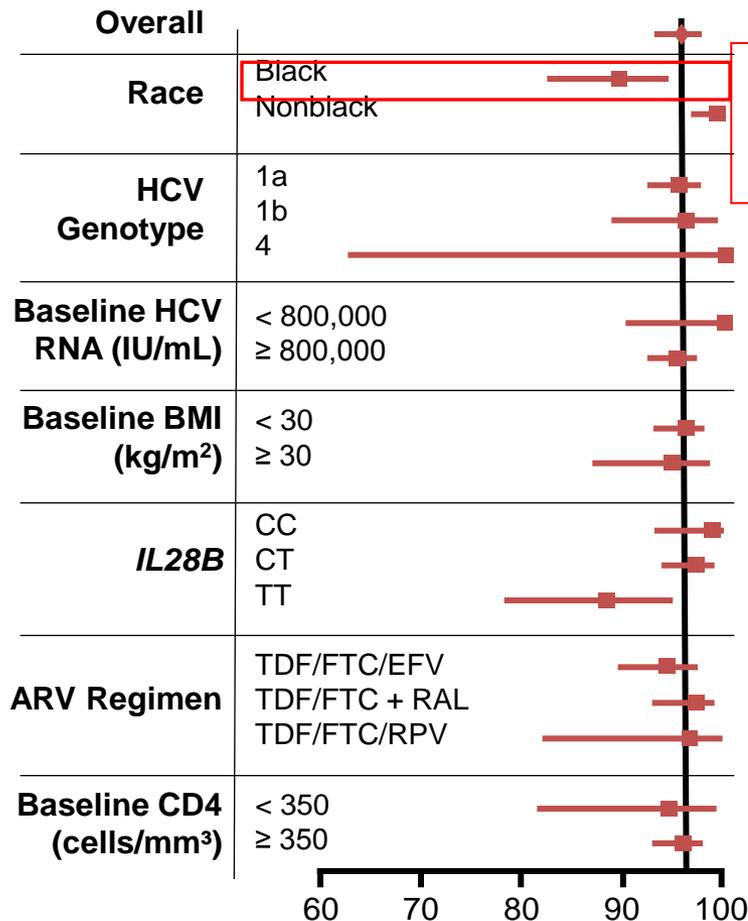
ION-4: LDV/SOF for 12 Wks in GT1/4 HCV/HIV-Coinfected Pts

- **Very high SVR12 rate**
 - **No differences based on HCV treatment experience or cirrhosis status**
- **Black (vs nonblack) race associated with significantly lower SVR12 rate in multivariate analysis**
 - **10 relapses, all in black pts**



ION-4: LDV/SOF Effective Across All Pt Demographic and Disease Subgroups

SVR12, % (95% CI)



- 10 relapses all in black pts
- No pt with HIV virologic rebound
- No discontinuation of therapy due to adverse events
- 4 pts experienced increase in creatinine > 0.4 mg/dL
 - 2 completed treatment without change in ART
 - 1 pt changed TDF to new NRTI
 - TDF dose reduced in 1 pt



ION-4: Resistance Analysis and LDV/SOF Drug-Drug Interactions With bPIs

- **Deep sequencing at BL identified 67 (20%) pts with NS5A RAVs^[1]**
 - **63 (94%) of these pts achieved SVR12**
- **RAVs in NS5A found in 10/12 pts with virologic failure**
- **No S282T mutation in NS5B found in any pt at BL or virologic failure**
- **In drug-drug interaction studies with LDV/SOF and boosted PIs and TFV^[2]**
 - **LDV/SOF increases ATV, RTV, and TFV exposure**
 - **ATV/RTV + TDF/FTC increases LDV**
 - **DRV/RTV + TDF/FTC decreases SOF**
- **Staggered administration did not mitigate interactions but interactions not deemed clinically relevant**

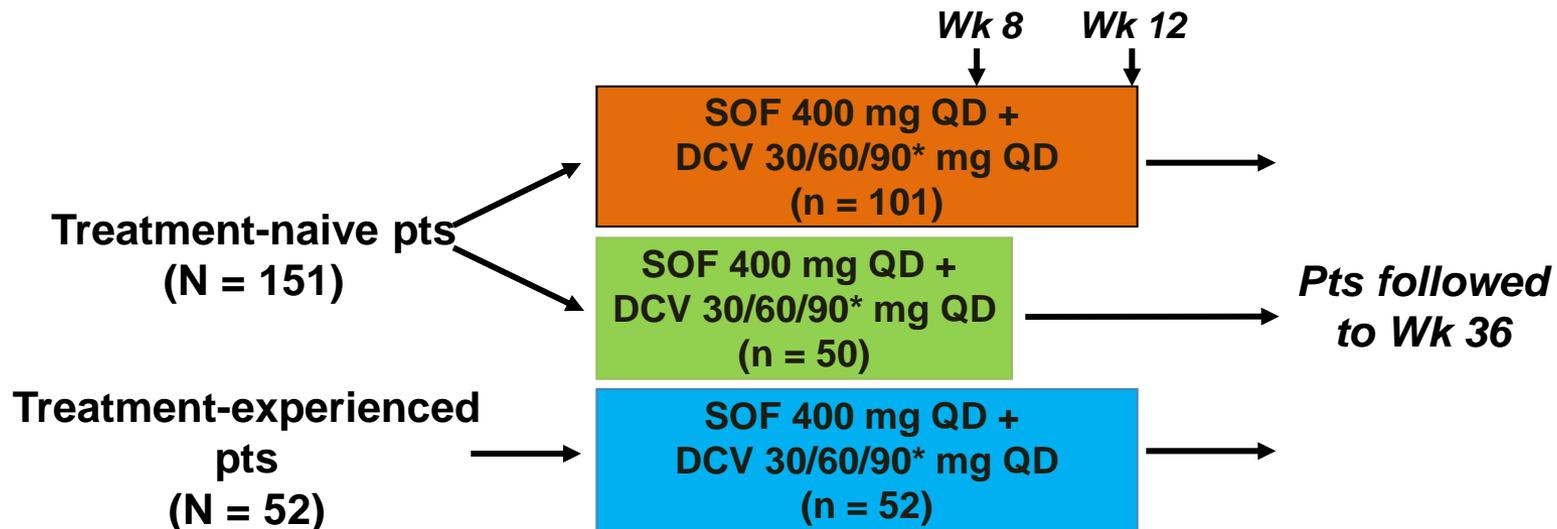
ERADICATE: SOF/LDV in ARV-Treated and Untreated HCV/HIV-Coinfected Patients

- **Single-arm phase II trial in GT1, HCV treatment-naive, coinfecting pts**
 - **ARV-untreated pts: stable CD4+ and HIV-1 RNA < 500 c/mL, or CD4+ > 500 cells/mm³;**
 - **ARV-treated patients: CD4+ > 100 cells/mm³, HIV-1 RNA < 40 c/mL, stable ARV regimen for ≥ 8 wks (TDF, FTC, EFV, RPV, RAL only)**
- **Primary endpoint: SVR12**
- **ARV use in 37 ARV-treated patients: EFV (41%), RAL (27%), RPV (21%), RPV and RAL (8%), EFV and RAL (3%)**



ALLY-2: SOF + DCV in GT1-6 HCV/HIV-Coinfected Pts

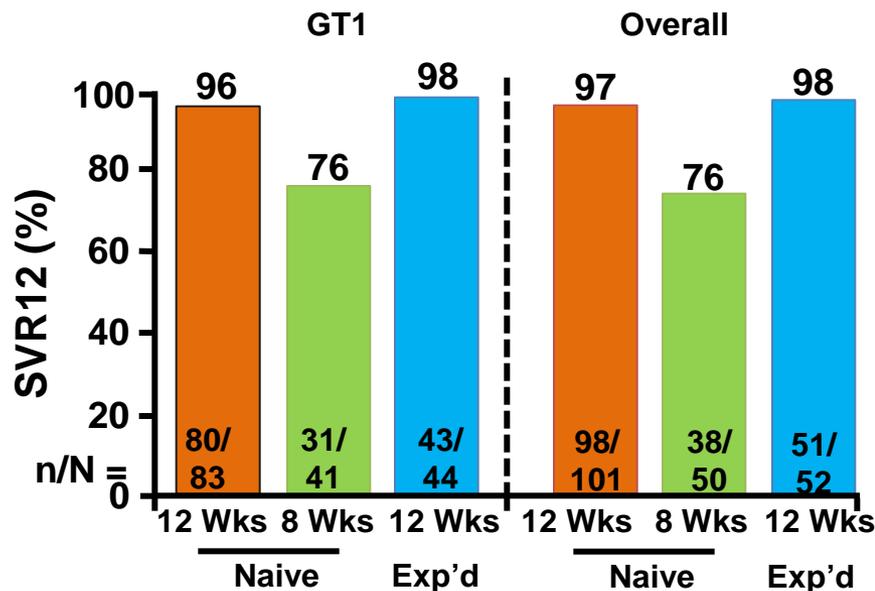
- **Open-label phase III study**
 - Non-GT1 < 20% in each cohort; compensated cirrhosis < 50% overall; HIV-1 RNA < 50 c/mL and CD4+ ≥ 100 in pts on ART; CD4 ≥ 350 in pts not on ART
 - ART allowed: PI/RTV, NRTIs, NNRTIs, INSTIs, MVC, ENF
- **Primary endpoint: SVR12 in GT1 naive pts treated for 12 wks**



*Standard dose of 60 mg adjusted for ART: 30 mg with RTV; 90 mg with NNRTIs except RPV.

ALLY-2: Virologic Outcomes With SOF + DCV in HIV/HCV-Coinfected Pts

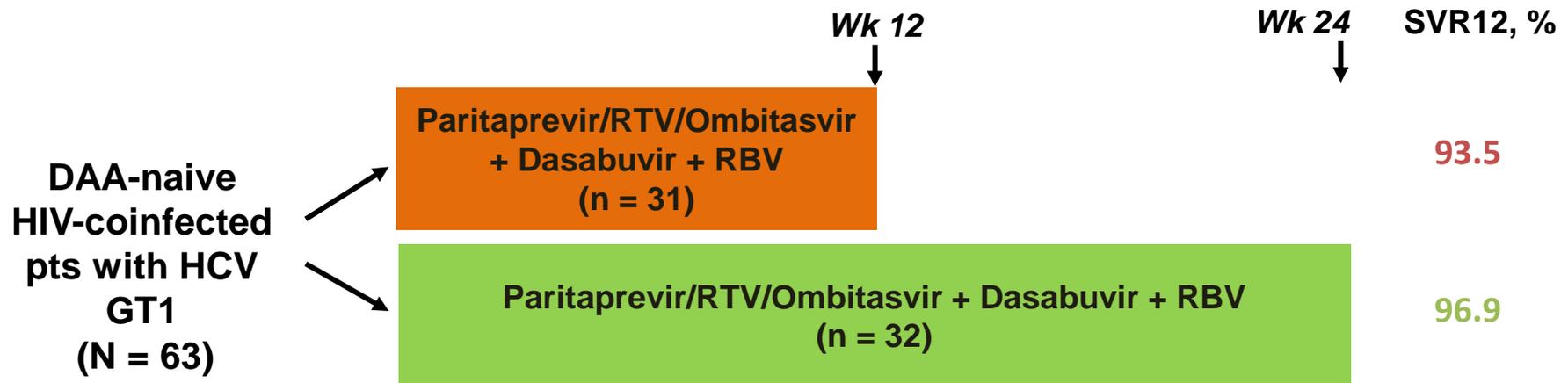
- High SVR12 rates with 12 wks SOF + DCV
 - Large decline in SVR rate with shortening to 8 wks



- In 12-wk groups analyzed by GT, 100% with SVR12 except GT1a
 - GT1a naive: 96%; exp'd: 97%
- Similar SVR12 rates in pts with or without baseline NS5A RAVs
- 12 pts with relapse, 10 in 8-wk arm
 - 1 in 8-wk arm had emergent NS5A RAVs
- No NS5B RAVs at BL or time of failure
- No discontinuation of therapy due to AEs
- 10 pts with HIV-1 RNA > 50 at EOT
 - 8 with repeat testing; 7 with suppression without change in ART; 1 with HIV-1 RNA of 59; 2 LTFU
- 2 with HIV VF = HIV-1 RNA ≥ 400 c/mL

TURQUOISE I: Paritaprevir/RTV/Ombitasvir + Dasabuvir + RBV in GT1 HCV/HCV Pts

- Open-label phase II/III trial in GT1, DAA-naive, coinfectd pts
 - HIV-1 RNA < 40 c/mL on ATV or RAL regimen; CD4+ count ≥ 200 or CD4+% ≥ 14%
- Primary endpoint: SVR12
- 19% of patients per arm had cirrhosis



Paritaprevir/RTV/ombitasvir 150/100/25 mg QD FDC; dasabuvir 250 mg BID; RBV 1000-1200 mg/day.

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C-EDGE Coinfection: Grazoprevir/Elbasvir for Pts Coinfected With HCV/HIV

- **Multicenter, single-arm, open-label phase III trial**



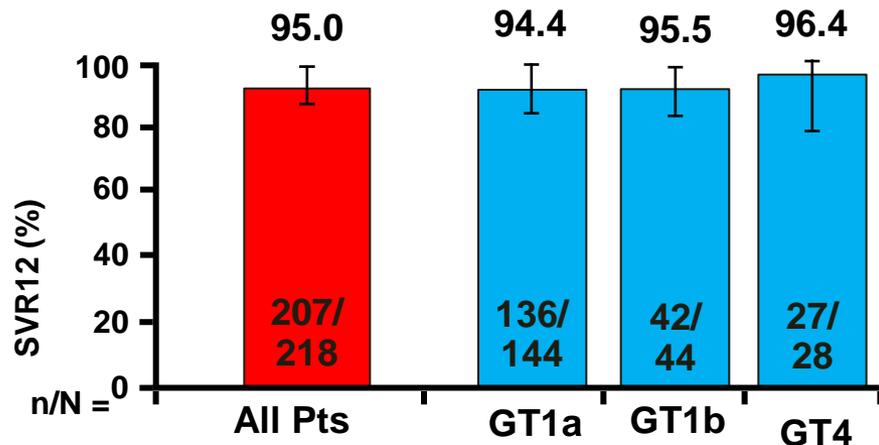
Coformulated grazoprevir/elbasvir dosed orally 100/50 mg once daily

- **66% with GT1a HCV, 60% had HCV RNA > 800,000 IU/mL, 16% cirrhotic**

Baseline ART	
Undetectable HIV-1 RNA on ART (%)	96.8
▪ Abacavir containing	21.6
▪ Tenofovir DF containing	75.2
▪ Raltegravir	51.8
▪ Dolutegravir	27.1
▪ Rilpivirine	17.4

C-EDGE Co-infection: Key Findings

SVR12 With 12 Wks GZR/EBV According to Genotype



- No subgroup provided an efficacy advantage or disadvantage
- New NS3, NS5A RAVs detected at failure in 5 of 6 pts who relapsed
- Short-lived HIV-1 RNA increases occurred in 2 pts on ART during grazoprevir/elbasvir treatment: both resuppressed HIV-1 RNA without change of ART
- During 12 wks of treatment, no significant changes in CD4+ cell count (n = 207)
- Grazoprevir/elbasvir well tolerated: no pt discontinued for AEs and no serious treatment-related AEs

LTFU or DC*	4	3	1	0
Breakthrough	0	0	0	0
Relapse	6	4	1	1
Reinfection	1	1	0	0

*Unrelated to virologic failure.



Conclusions

- **Large numbers of patients co-infected with HIV and Hepatitis C with more rapid disease course**
 - **Treat all HIV/HCV Co-infected Patients**
- **SVR12 “cure” rates are high using DAA only therapy**
 - **No difference in HCV monoinfected and HIV/HCV co-infected patients**
- **Attention to Drug Interactions between HIV ARVs and DAAs prior to initiating therapy**

Thank You



Acknowledgements
