HIV & HCV – Applying Old Lessons To A New Foe

7th Annual Arizona Infectious Disease Conference (AZID)
Black Canyon Conference Center in Phoenix, AZ,
July 26-28, 2016

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Creighton University Medical School

Dignity Health Medical Group Arizona

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

- **Dr. Kohli has been a speaker for Merck and consultant for Gilead and Alexion**

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**
- **Practical Concerns**
- **The Lessons of Advocacy**

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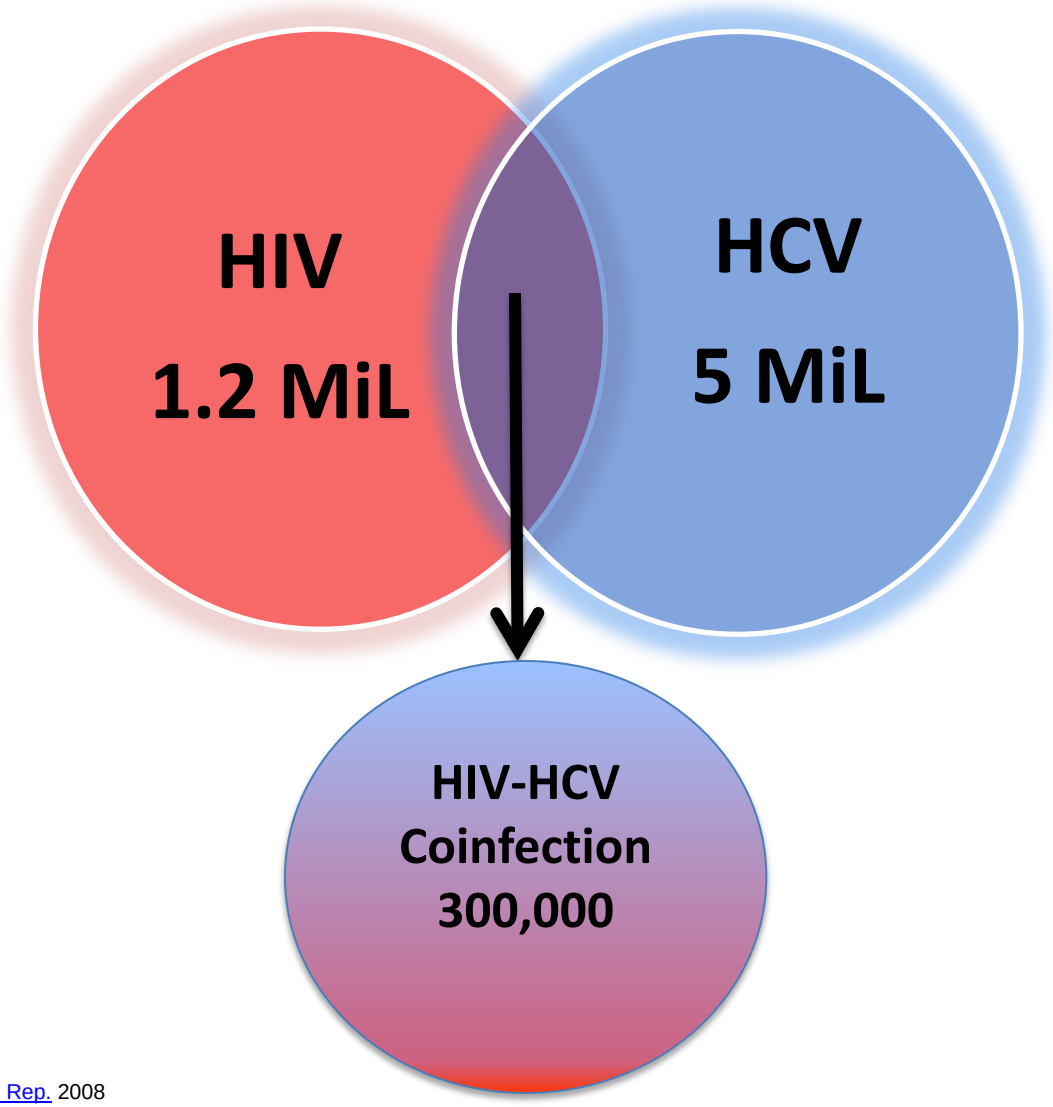
HCV Infection

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

Epidemic of HIV and HCV in US



Weinbaum CM et al. MMWR Recomm Rep. 2008
CDC. HIV Surveillance Report, 2013; vol 25. Published February 2015. http://www.cdc.gov/hiv/pdf/g-l/hiv_surveillance_report_vol_25.pdf (Accessed on May 20, 2015).
CDC March 2014. http://www.cdc.gov/hiv/pdf/library_factsheets_HIV_and_viral_Hepatitis.pdf

Transmission of Hepatitis C

Sexual Transmission of Hepatitis C

Curr Infect Dis Rep (2010) 12:118–125
DOI 10.1007/s11908-010-0088-1

Epidemic of Sexually Transmitted Hepatitis C Virus Infection Among HIV-Infected Men

Daniel Seth Fierer

Published online: 23 February 2010
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SURVEILLANCE AND OUTBREAK REPORTS

Hepatitis C virus infection in HIV-infected men who have sex with men: sustained rising incidence in Antwerp, Belgium, 2001–2009

E Bottieau (ebottieau@itg.be)[1], L Apers[1], M Van Esbroeck[1], M Vandenbruaene[1], E Florence[1]
1. Department of Clinical Sciences, Institute of Tropical Medicine, Antwerp, Belgium

Citation style for this article:
Bottieau E, Apers L, Van Esbroeck M, Vandenbruaene M, Florence E. Hepatitis C virus infection in HIV-infected men who have sex with men: sustained rising incidence in Antwerp, Belgium, 2001–2009.
Euro Surveill. 2010;15(39):pii=19673. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19673

Article published on 30 September 2010

Journal of Clinical Virology 49 (2010) 65–68

Contents lists available at ScienceDirect

Journal of Clinical Virology

journal homepage: www.elsevier.com/locate/jcv

Case report

Acute hepatitis C infection with evidence of heterosexual transmission

Oanh Nguyen[a], Vicky Sheppeard[a], Mark W. Douglas[b], Elise Tu[c], William Rawlinson[c,*]

[a] Centre for Population Health, Sydney West Area Health Service, Sydney, Australia
[b] Storr Liver Unit, Westmead Millennium Institute and University of Sydney, Sydney, Australia
[c] Virology, SEALS Department of Microbiology, Prince of Wales Hospital, Randwick, NSW 2031, Australia

NOTE

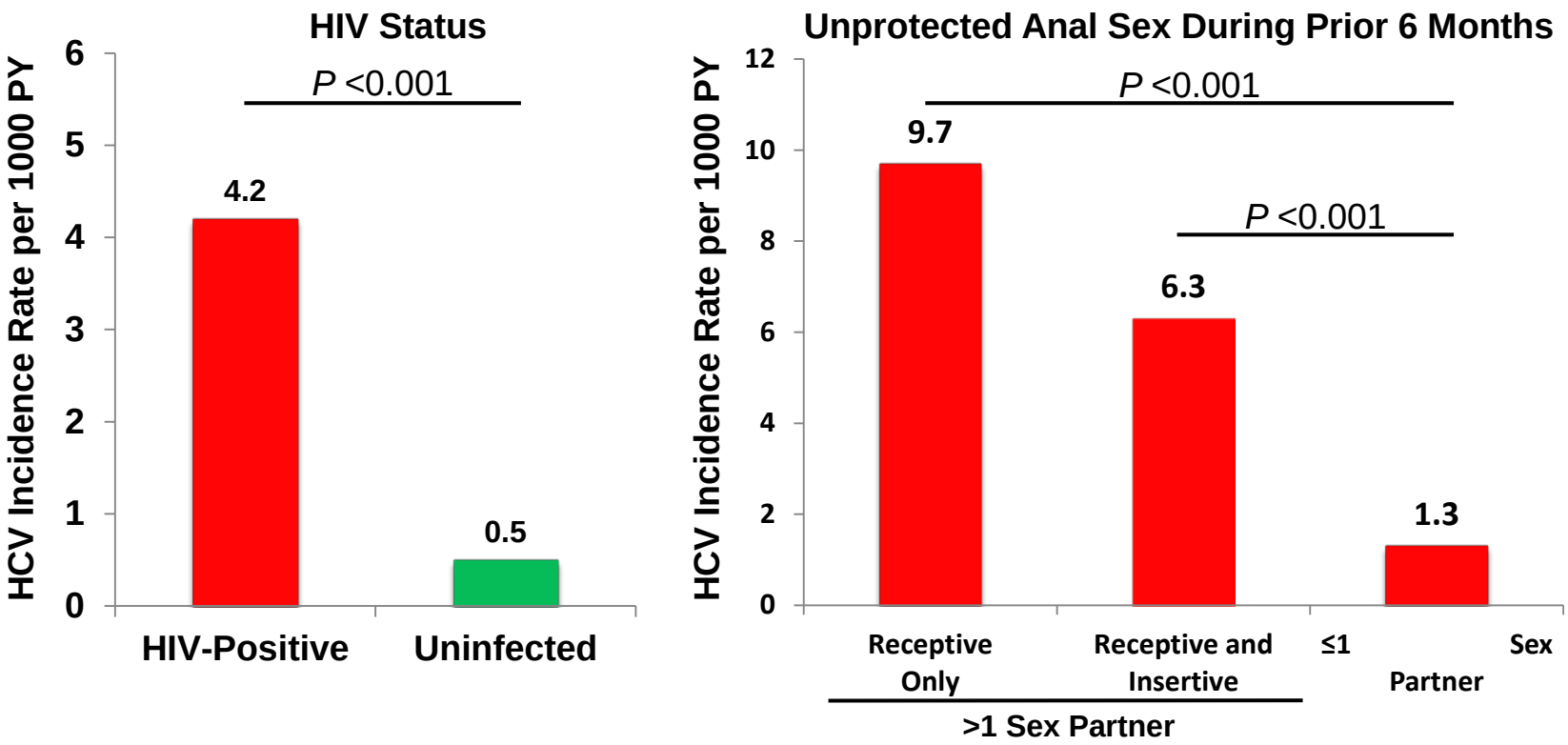
Sexual Transmission of Hepatitis C Virus in Human Immunodeficiency Virus-Negative Men Who Have Sex With Men: A Series of Case Reports

Thijs J. W. van de Laar, PhD,† William A. Paxton, PhD,†‡ Fokla Zorgdrager, BSc,†‡ Marion Cornelissen, PhD,†‡ and Henry J. C. de Vries, MD, PhD†§¶*

Sexually Transmitted Diseases • Volume 38, Number 2, February 2011
I Diseases Association. Unauthorized reproduction of this article is pro

Incidence of HCV Infection Is Associated With HIV-Positive Status and Unprotected Sex

HCV Incidence Rate in 5310 MSM
(A Prospective Cohort Analysis, 1984-2011)



Among HIV-positive patients, each 100 cells/mm^3 increase in CD4 cell count was associated with a 7% (*P* =0.002) decrease in the HCV incidence rate up to a CD4 count of 500 cells/mm^3

PY, person-years.
Witt MD, et al. *Clin Infect Dis*. 2013;57:77–84.

How Often to Test HIV+ MSM for (Re)-Infection?

AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

AASLD

IDSA

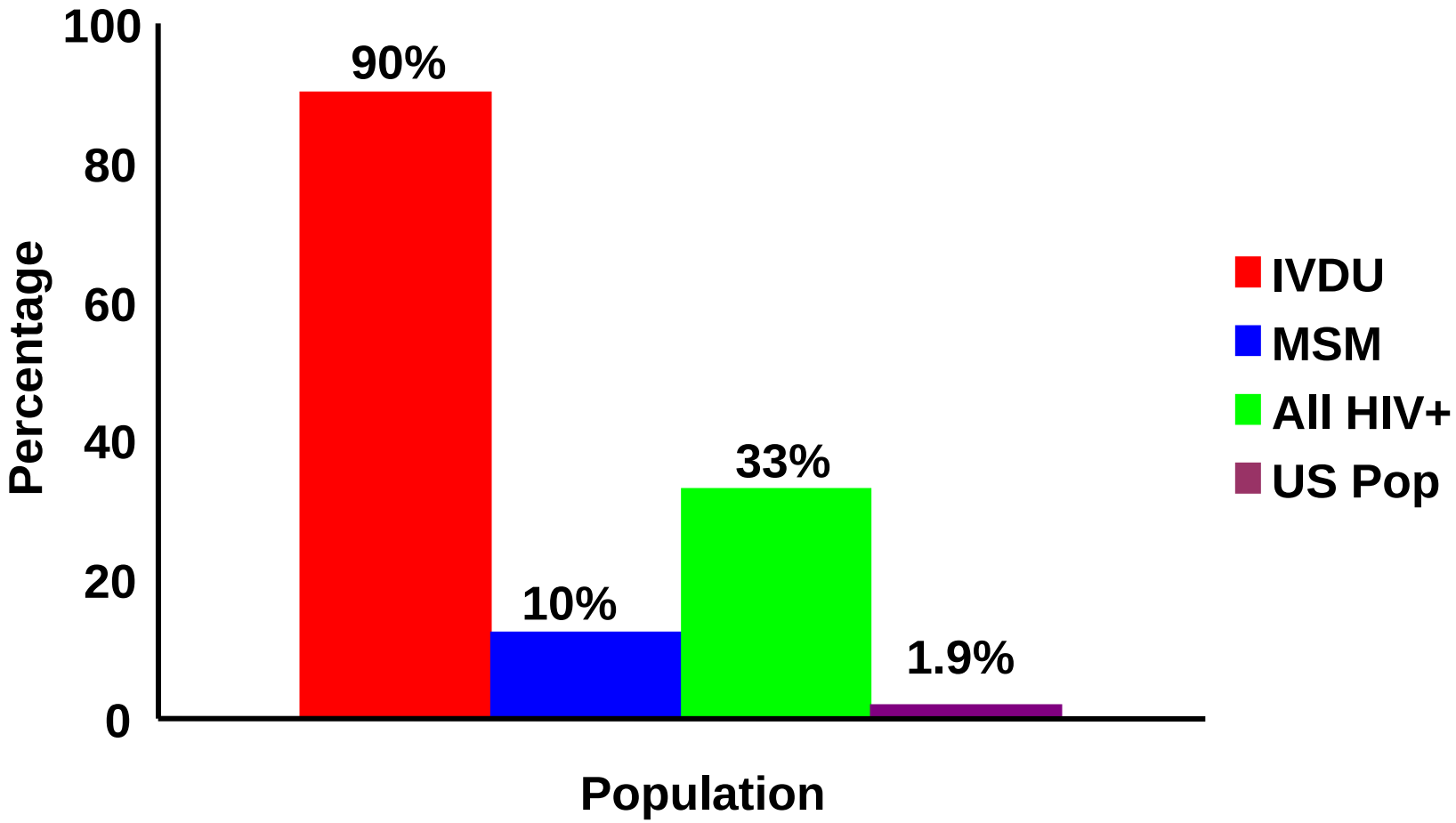
Infectious Diseases Society of America

Annual HCV testing is recommended for persons who inject drugs and for HIV-seropositive men who have unprotected sex with men. Periodic testing should be offered to other persons with ongoing risk factors for exposure to HCV.

Rating: Class IIA, Level C

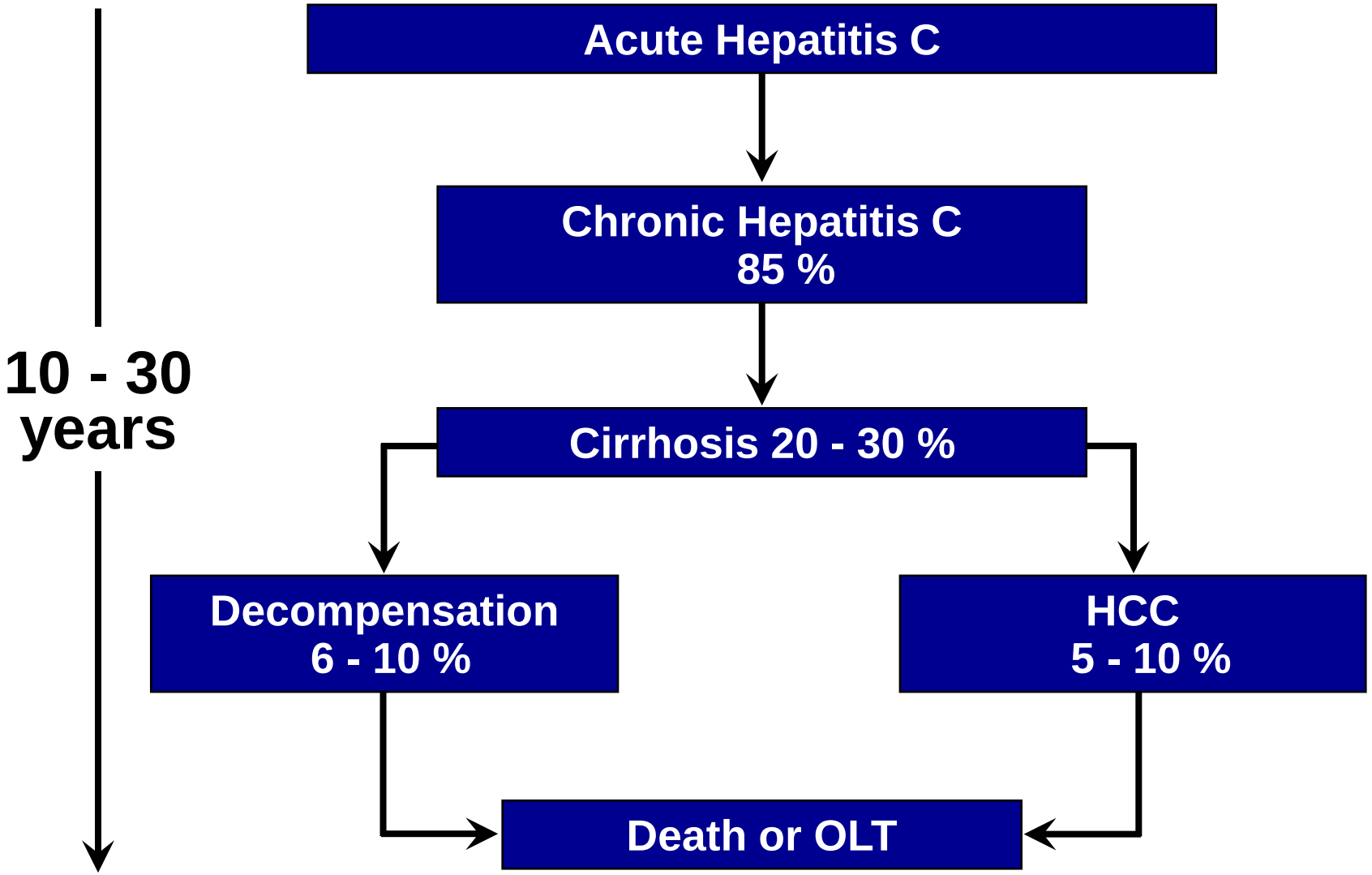
Source: Kieffer TA, et al. J Antimicrob Chemother. 2010:65:2012-12

Prevalence of HCV/HIV Co-infection

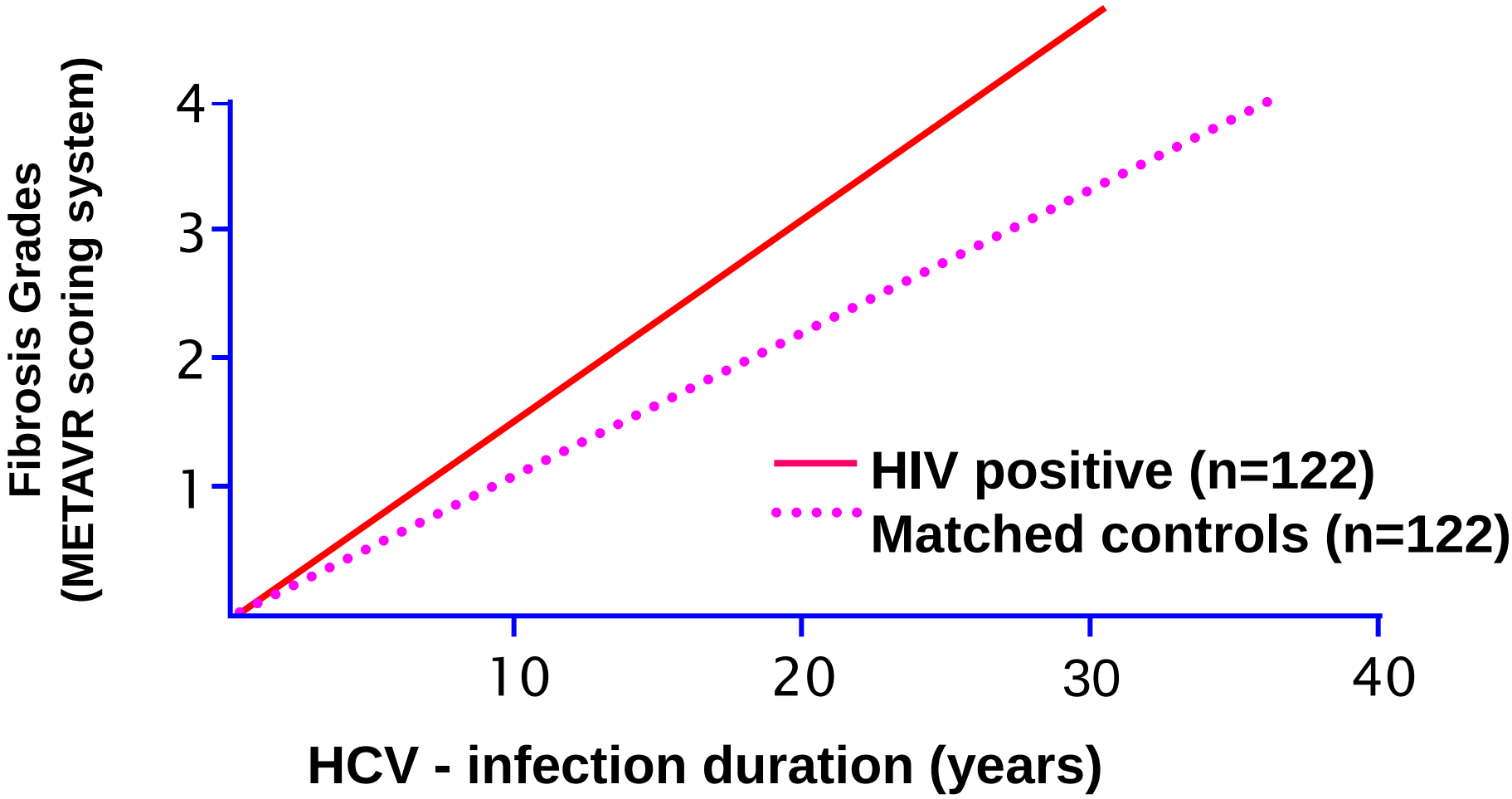


Sulkowski MS, Mast EE, Seeff, LB et al. Hepatitis C Virus Infection as an Opportunistic Disease in Persons infected with Human Immunodeficiency Virus. *Clin Infect Dis.* 2000;30:577-84.

Natural History of Hepatitis C

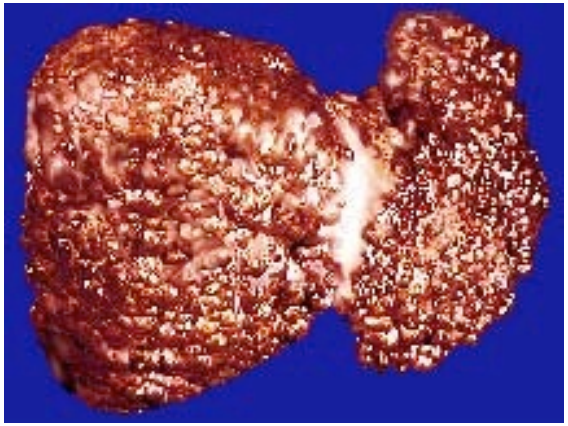


HIV Coinfection Accelerates Liver Fibrosis Progression Rate



Benhamou Y. Hepatology 1999;30:1054

HIV Coinfection Accelerates Liver Fibrosis Progression Rate



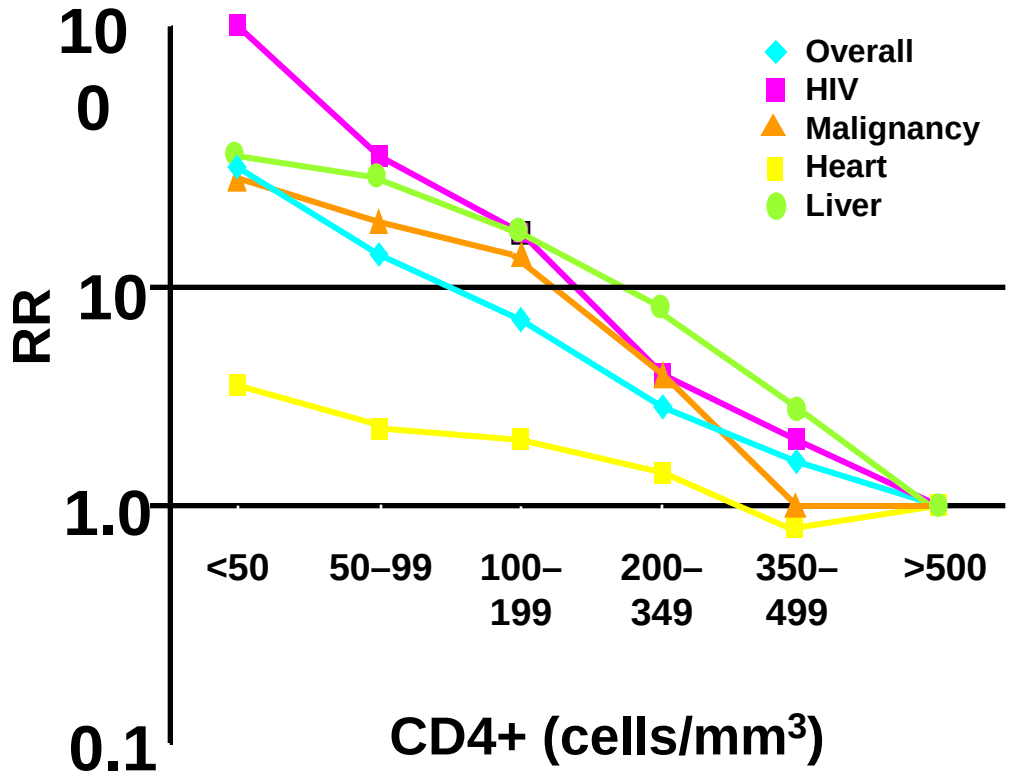
- 1.4-fold increase in fibrosis progression rate
- 3-fold increase in development of advanced fibrosis
- Case-reports of hyper-acute progression (infection to cirrhosis and death in 5 yrs)

Qu J et al *BMC Immunol* 2012; 13(15):1-12; Thomas DL et al *JAMA* 2000;284(4):450-456; Mohsen AH et al *Gut*. 2003;52(7):1035-40

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



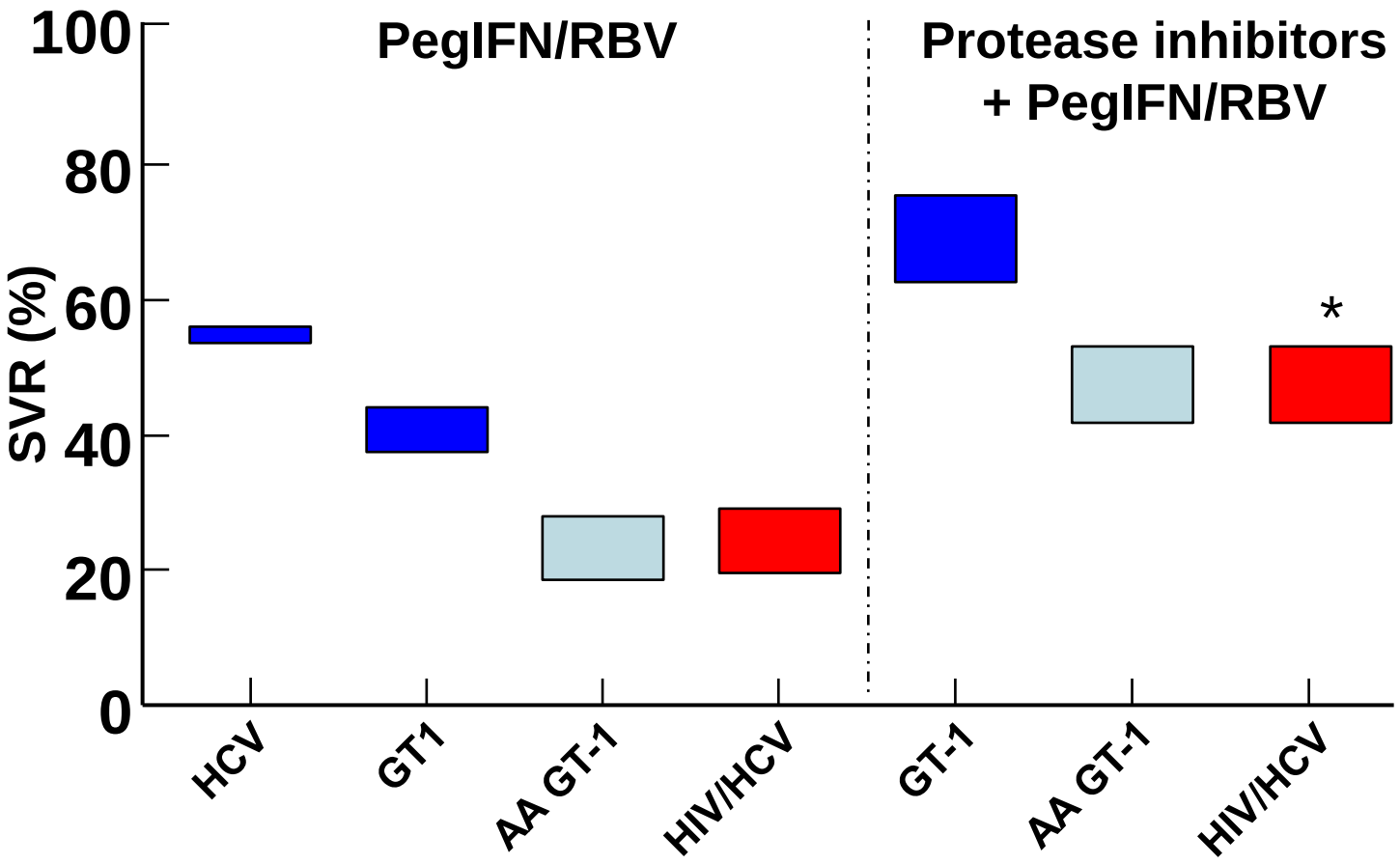
Weber R et al. *Arch Intern Med.2006, 166:1632-41.*

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

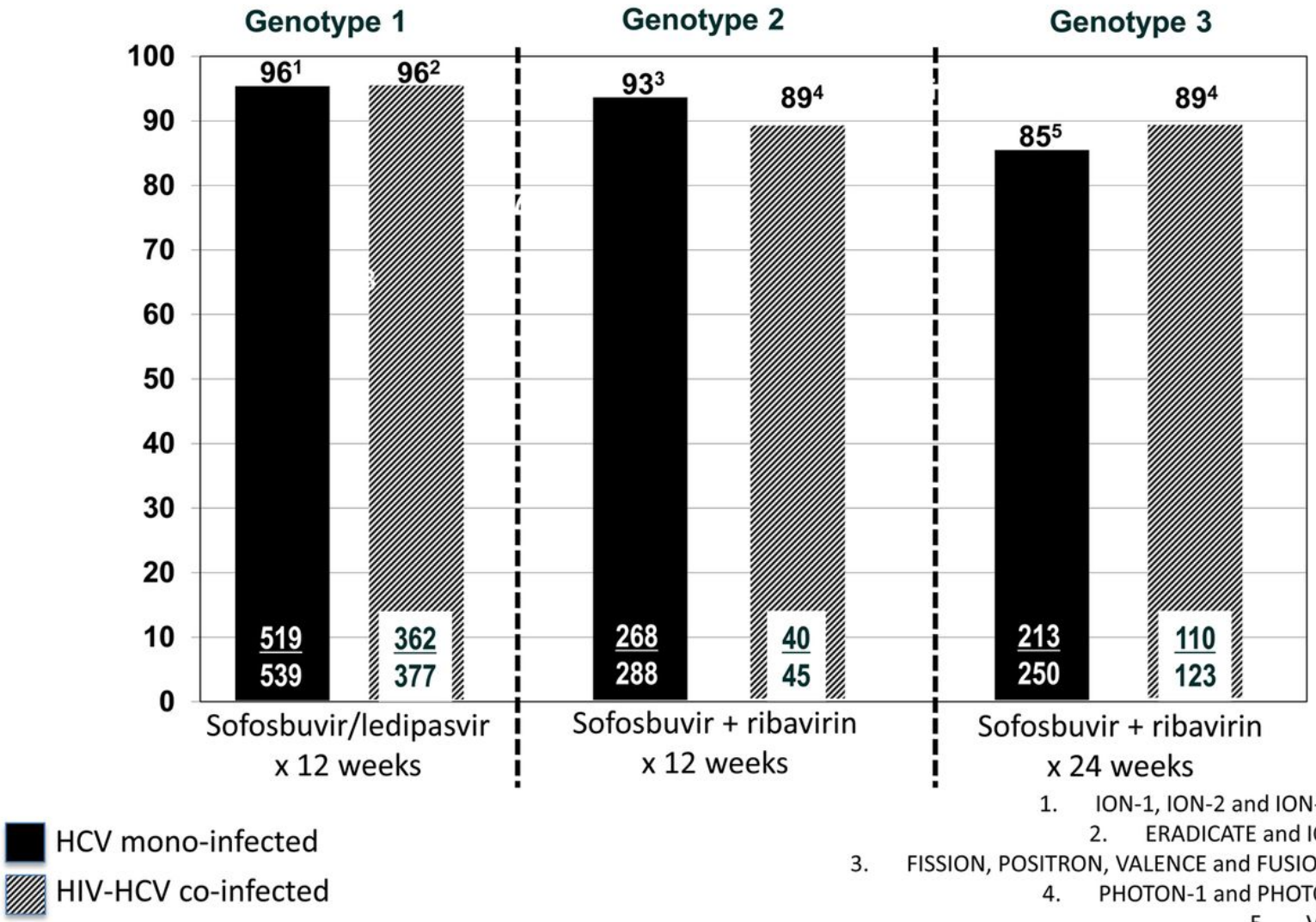
Adapted from Soriano V, JAC 2008; 62

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



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]

Stephen D. Shafran Clin Infect Dis. 2015;61:1127-1134

Overview

- The problem of hepatitis C in HIV patients
- **Recently approved directly acting agents with data for HIV patients**
- Practical Concerns
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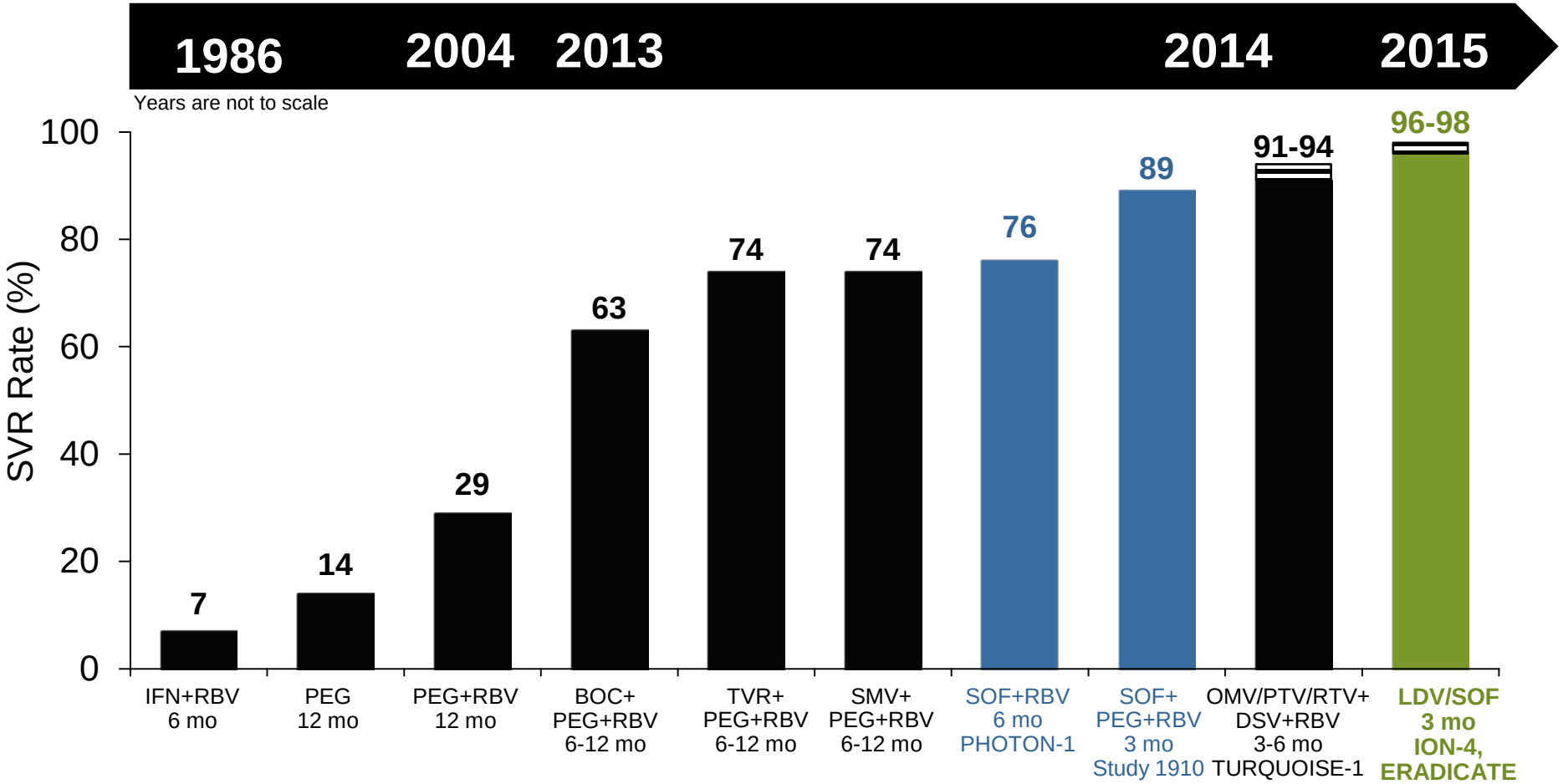
SVR Rates for Approved Therapies in HIV/HCV GT 1 Patients



2015 AASLD/IDSA Guidance: "HIV/HCV co-infection should receive the same treatment as recommended for HCV mono-infection"

Dieterich D et al. CROI 2014; P#24; Rodriguez-Torres M et al. IDWeek 2013; P#714; Sulkowski M et al. Lancet Infect Dis 2013;13:597–605; Sulkowski M et al. Ann Intern Med 2013;159:86–96; Sulkowski M et al Lancet 2014;314:653–61; Sulkowski M et al. AIDS 2014; P#104 LB; Torriani FJ, et al. N Engl J Med 2004;351:438–50; AASLD/IDSA/IAS–USA. Recommendations for testing, managing, and treating hepatitis C. http://www.hcvguidelines.org. Accessed January 15, 2015

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 coinfected 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)**

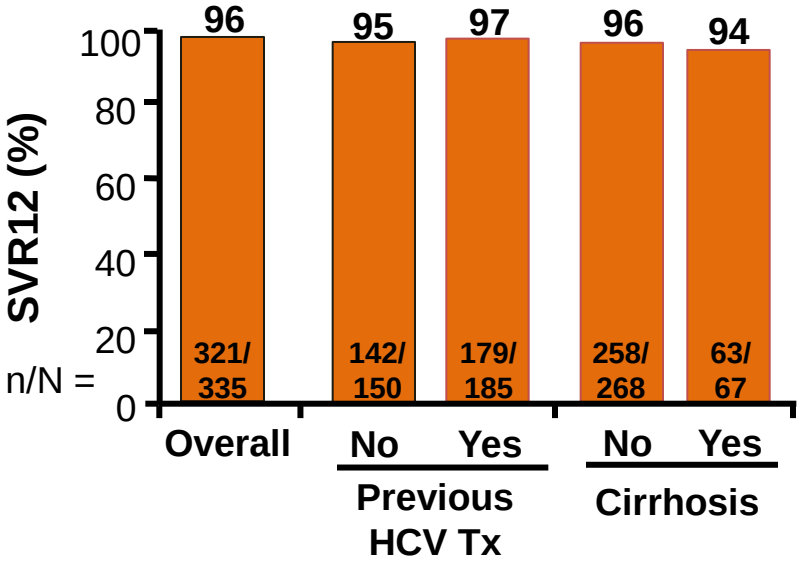
- **HCV treatment experienced: 55%**
  - **Previous HCV PI therapy: 29%**

Cooper C, et al. EASL 2015. Abstract P1353..

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**

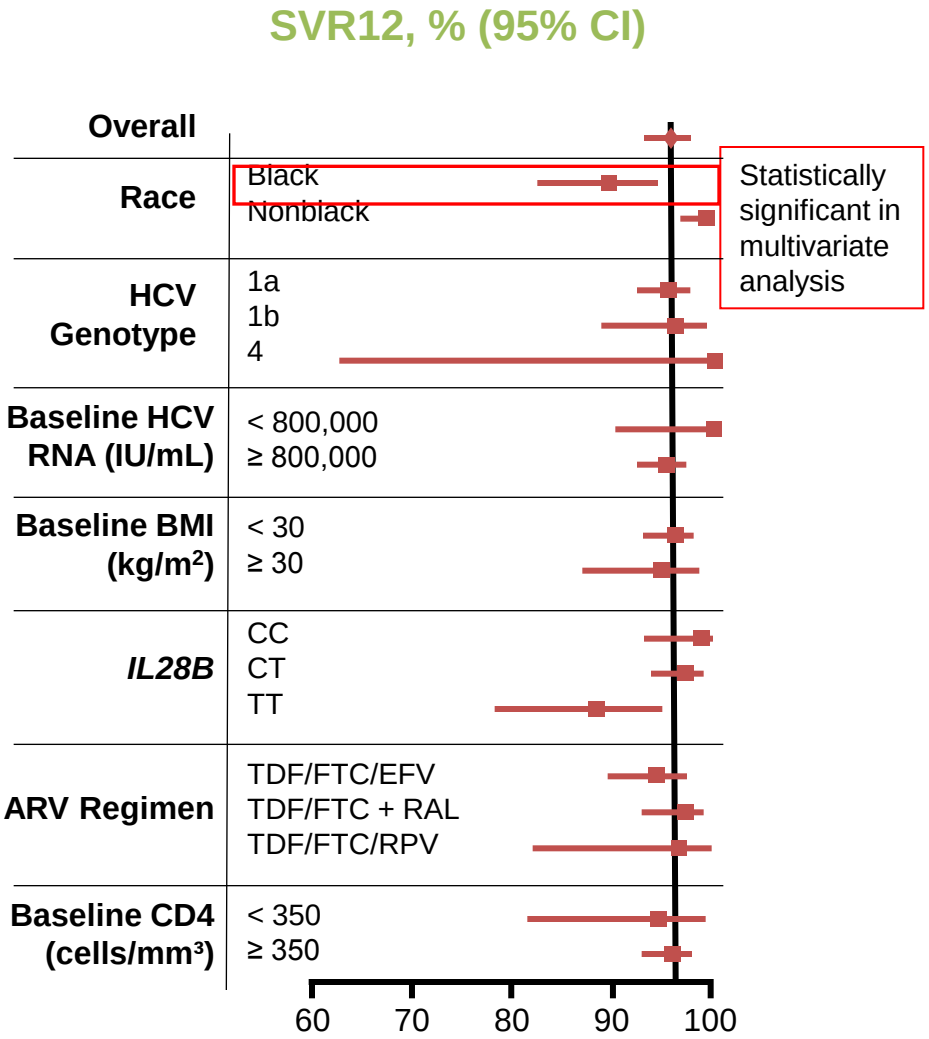
- **Black (vs nonblack) race associated with significantly lower SVR12 rate in multivariate analysis**
  - **10 relapses, all in black pts**



Cooper C, et al. EASL 2015. Abstract P1353..

SVR Rates According to BL Characteristics

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



- **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**

Naggie S, et al. CROI 2015. Abstract 152LB.

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**

Naggie S, et al. CROI 2015. Abstract 152LB.
German P, et al. CROI 2015. Abstract 82.

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

- **Single-arm phase II trial in GT1, HCV treatment-naive, coinfected pts**
  - **ARV-untreated pts: stable CD4+ and HIV-1 RNA < 500 c/mL, or CD4+ > 500 cells/mm^3;**
  - **ARV-treated patients: CD4+ > 100 cells/mm^3, HIV-1 RNA < 40 c/mL, stable ARV regimen for ≥ 8 wks (TDF, FTC, EFV, RPV, RAL only)**

- **Primary endpoint: SVR12**

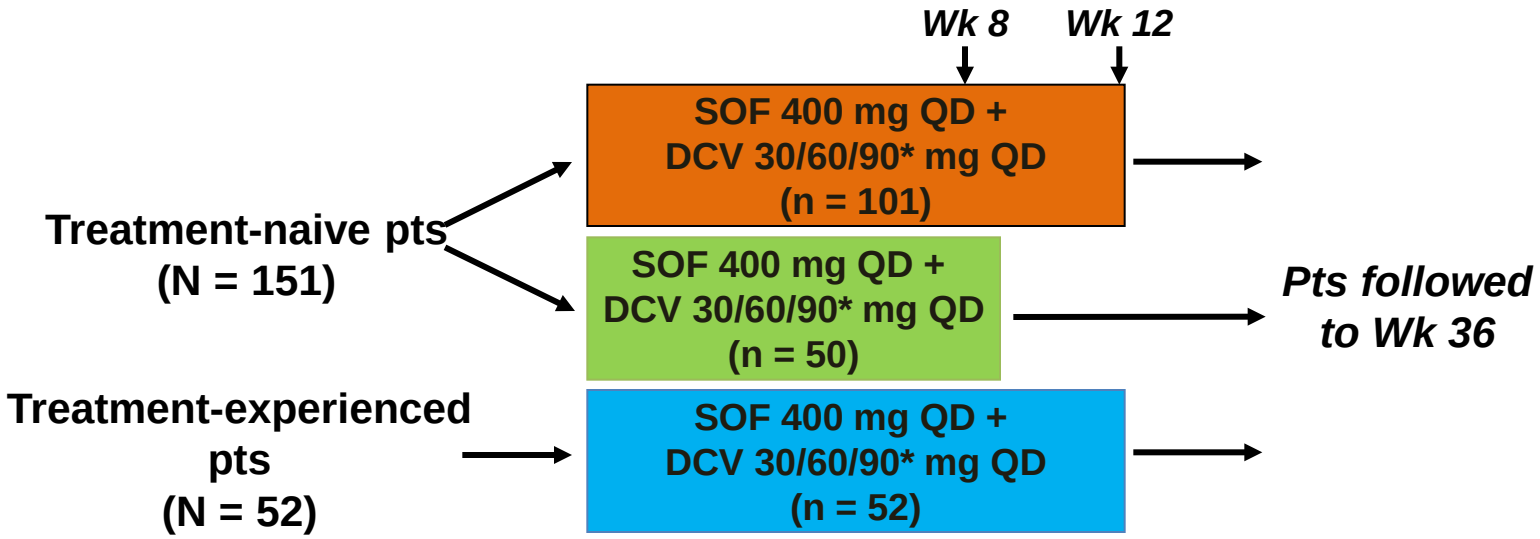
- **ARV use in 37 ARV-treated patients: EFV (41%), RAL (27%), RPV (21%), RPV and RAL (8%), EFV and RAL (3%)**

Sofosbuvir/ledipasvir 400/90 mg FDC tablet once daily.

Osinusi..Kohli et al. JAMA, march 2015

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**

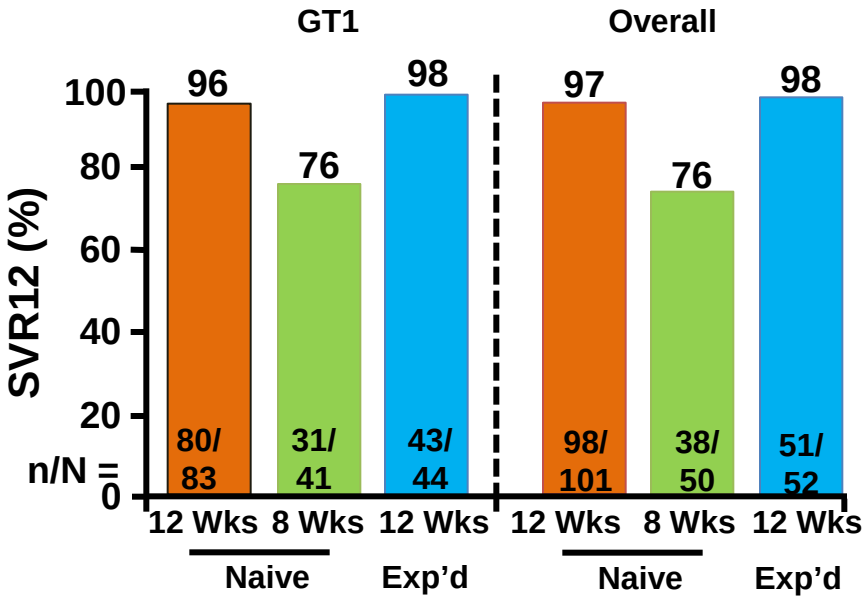


***Standard dose of 60 mg adjusted for ART: 30 mg with RTV; 90 mg with NNRTIs except RPV.**

Wyles DL, et al. CROI 2015. Abstract 151LB.

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

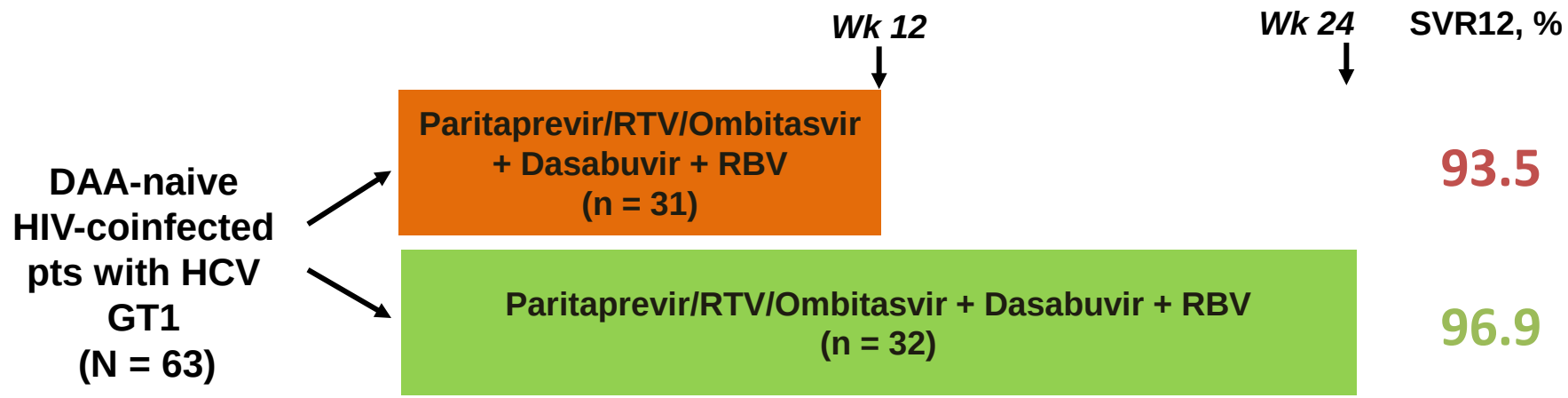


- In 12-wk groups analyzed by GT, 100% with SVR12 except GT1a
  - GT1a naive: 96%; exp'd: 97%
- Similar SVR12 rates in pts with or without baseline NS5A RAVs
- 12 pts with relapse, 10 in 8-wk arm
  - 1 in 8-wk arm had emergent NS5A RAVs
- No NS5B RAVs at BL or time of failure
- No discontinuation of 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

Wyles DL, et al. CROI 2015. Abstract 151LB.

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

- **Open-label phase II/III trial in GT1, DAA-naive, coinfected 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.

Sulkowski M, et al. AIDS 2014. Abstract MOAB0104LB

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

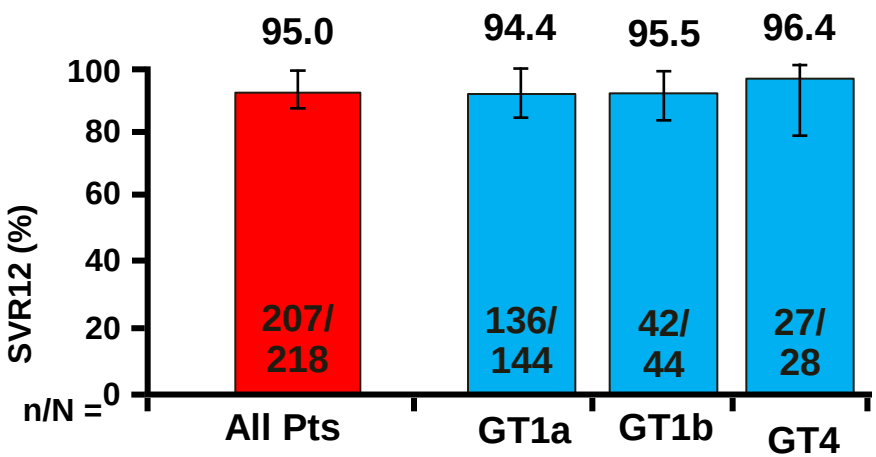
- **66% with GT1a HCV, 60% had HCV RNA > 800,000 IU/mL, 16% cirrhotic**

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

Rockstroh JK, et al. EASL 2015. Abstract P0887.

C-EDGE Co-Infection: Key Findings

SVR12 With 12 Wks GZR/EBV According to Genotype



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.

- 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

Rockstroh JK, et al. EASL 2015. Abstract P0887. Reproduced with permission.

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Contrasting the HIV & HCV Epidemics

Key Questions

- **What lessons in testing and linkage to care can be learned from the HIV Epidemic?**

- **Are there successful models of HIV care that can be applied to HCV care on a broad scale?**

HRSA Continuum of HIV Care

Continuum Engagement in Care

Not in Care ⟷ **Fully Engaged**

Unaware of HIV infection	Aware of HIV infection (not in care)	Receiving some medical care but not HIV care	Entered HIV care but lost to follow-up)	Cyclical or intermittent user of HIV care	Fully engaged in HIV care

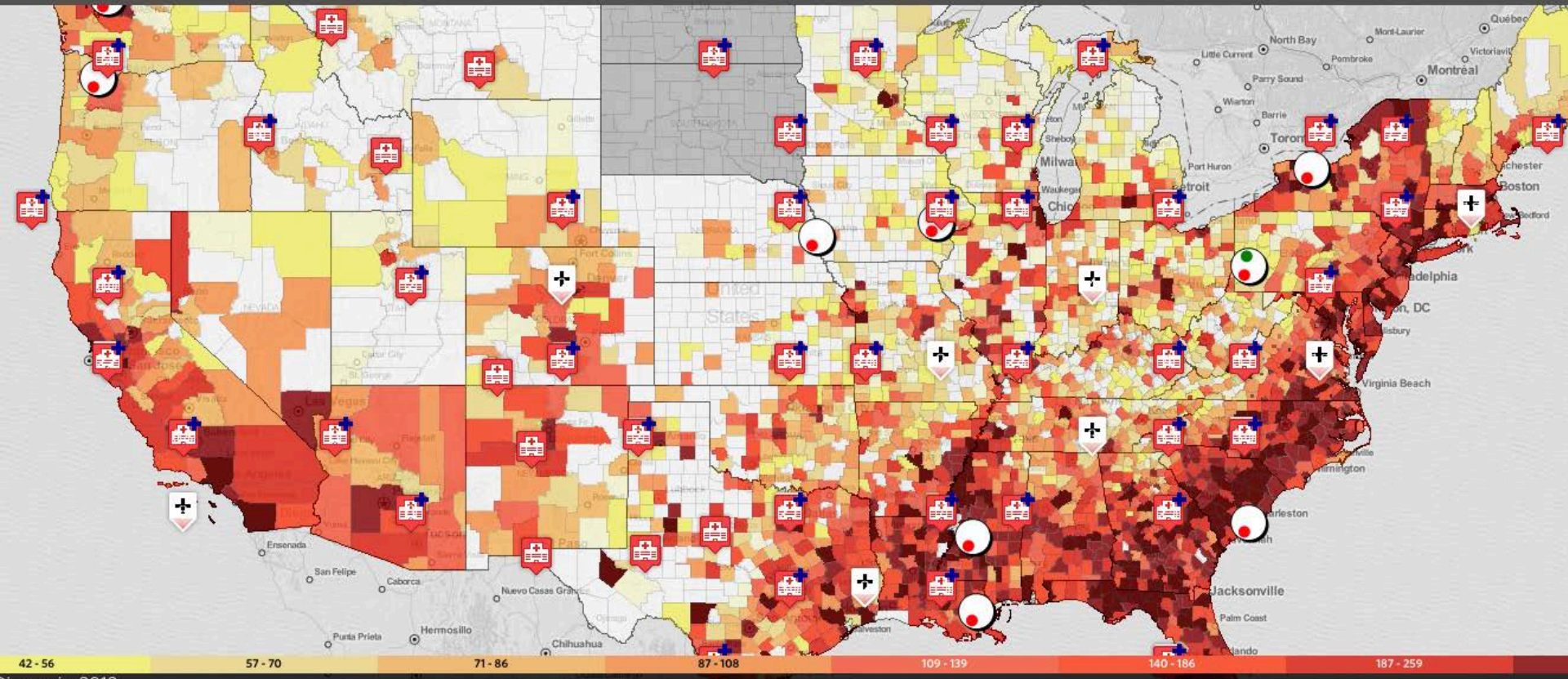
Source: Adapted from Cheever LW. Clin Infect Dis. 2007;44:1493-9.

AIDSVu

LOCAL STATISTICS

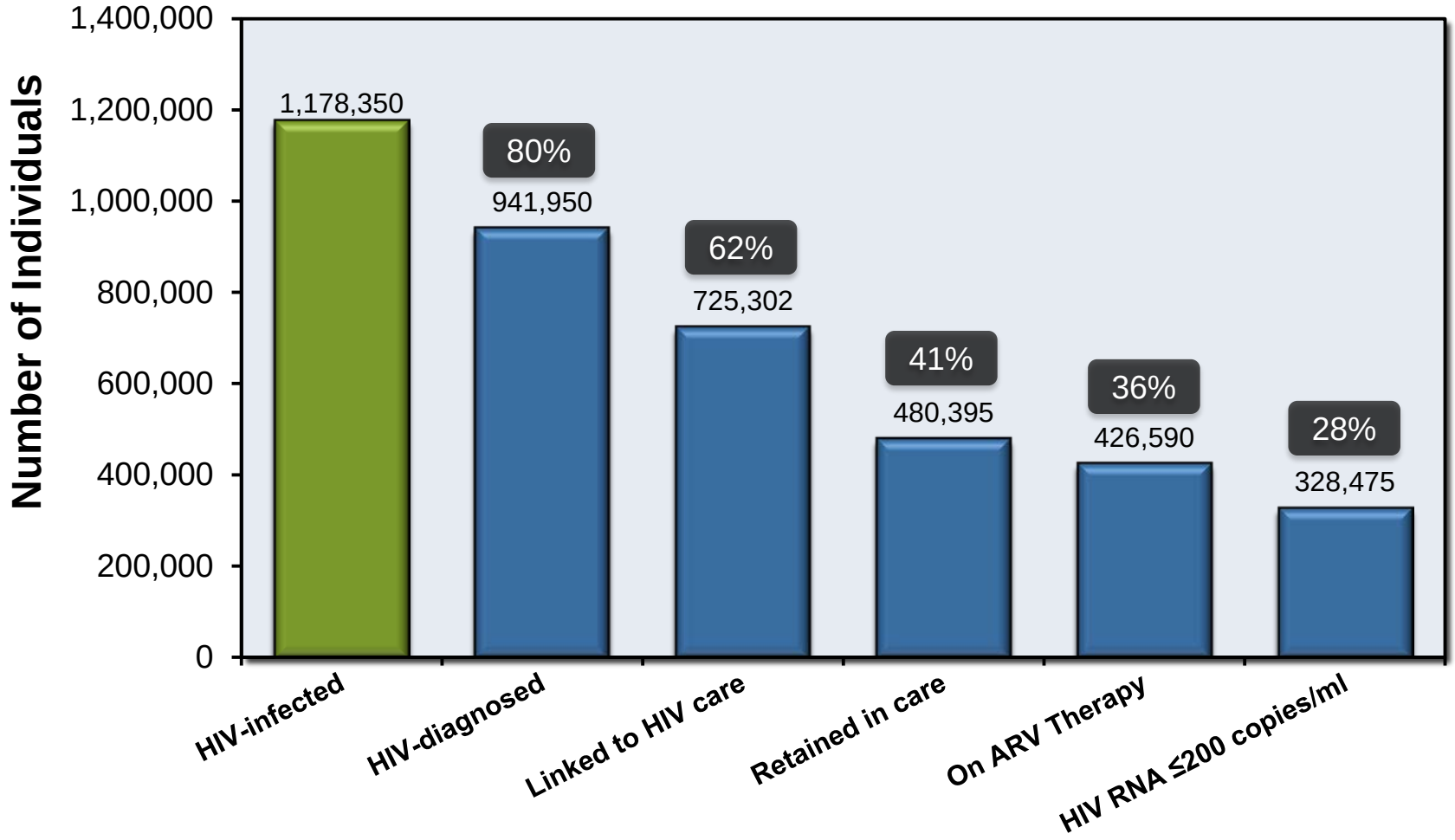
TESTING & CARE

RESOURCES



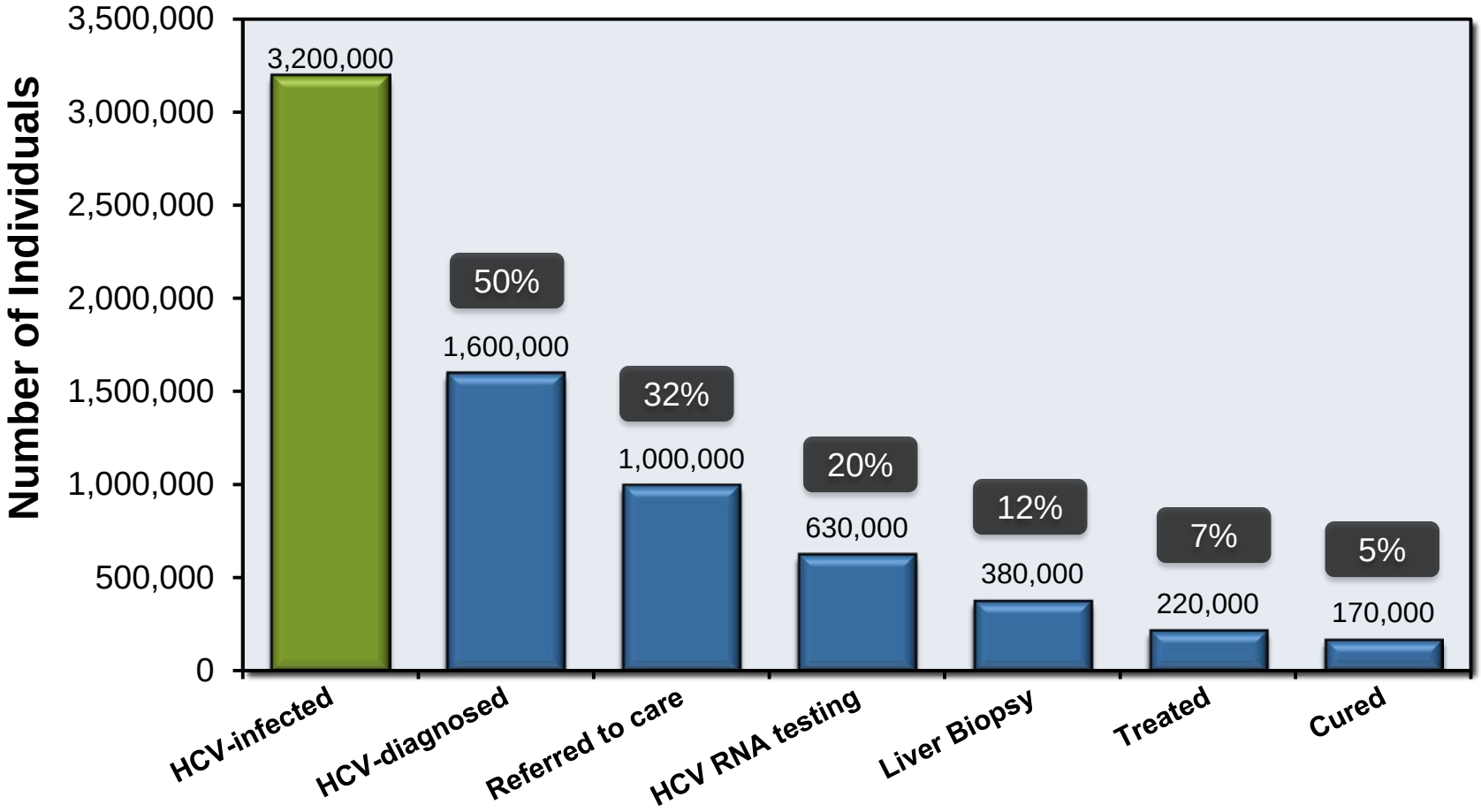
www.aidsvu.org

HIV Cascade of Care – United States



Cohen SM, et al. MMWR. 2011;60:1618-23

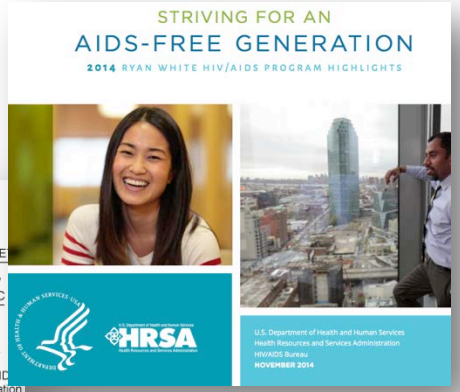
HCV Cascade of Care – United States

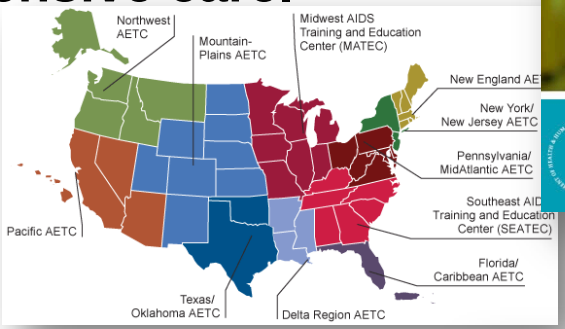


Source: Holmberg S, et al. NEJM. 2013;368:201859-61 .

Successful Models of HIV Care

- **Ryan White Care Act – Federally funded program ensuring that all with HIV infection receive meds *and* comprehensive care.**





- **AETC networks – Provider education**

- **Telehealth/Project ECHO – Provider mentoring, increasing pool of HIV treaters**

- **AAHIVM – Professional Certification, recognition of HIV expertise, advocacy**

AAHIVM
AMERICAN ACADEMY OF HIV MEDICINE

Practical Considerations

Treating the HIV/HCV Co-infected patient

Key Clinical Questions

- **How does HIV regimen influence HCV regimen selection (Drug-Drug Interactions)**
- **Which infection should be treated first?**

American Association for the Study of Liver Diseases
AASLD
IDSA
Infectious Diseases Society of America

Highest Priority for Treatment	
Advanced Fibrosis (F3-F4)	Class I, Level A
Organ Transplant	Class I, Level B
Mixed Cryoglobulinemia	Class I, Level B
Proteinuria, Nephrotic Syndrome, MPGN	Class IIa, Level B

High Priority for Treatment	
Moderate Fibrosis (F2)	Class I, Level B
HIV-1 co-infection	Class I, Level B
HBV co-infection	Class IIa, Level C
Coexistent liver disease (NASH)	Class IIa, Level C
Debilitating fatigue	Class IIa, Level B
Type II Diabetes Mellitus	Class IIa, Level B
Porphyria Cutanea Tarda	Class IIb, Level C

HIV/HCV Drug-Drug Interactions

HIV Entry/Integrase Inhibitors	Daclatasvir	Ledipasvir/Sofosbuvir	OBV/PTV/r + DSV	Simeprevir	Sofosbuvir
Dolutegravir	◇	◇	◇	◇	◇
Elvitegravir/cobicistat	□	□	●	●	◇
Raltegravir	◇	◇	◇	◇	◇
HIV NNRTIs	Daclatasvir	Ledipasvir/Sofosbuvir	OBV/PTV/r + DSV	Simeprevir	Sofosbuvir
Efavirenz	□	□	●	●	◇
Rilpivirine	◇	◇	□	◇	◇
HIV NRTIs	Daclatasvir	Ledipasvir/Sofosbuvir	OBV/PTV/r + DSV	Simeprevir	Sofosbuvir
Abacavir	◇	◇	◇	◇	◇
Emtricitabine	◇	◇	◇	◇	◇
Lamivudine	◇	◇	◇	◇	◇
Tenofovir	◇	□	◇	◇	◇
HIV Protease Inhibitors	Daclatasvir	Ledipasvir/Sofosbuvir	OBV/PTV/r + DSV	Simeprevir	Sofosbuvir
Darunavir	◇	◇	□	●	◇
Ritonavir	□	◇	●	●	◇

From www.hep-druginteractions.org

HIV/HCV Drug-Drug Interactions

	Simeprevir	Sofosbuvir	Ledipasvir	Daclatasvir	Paritaprevir, ritonavir, ombitasvir plus dasabuvir (PrOD)
Ritonavir-boosted atazanavir	No data	No data	Ledipasvir ↑; atazanavir ↑[a]	Daclatasvir ↑[b]	Paritaprevir ↑; atazanavir ↑
Ritonavir-boosted darunavir	Simeprevir ↑; darunavir ↔	Sofosbuvir ↑; darunavir ↔	Ledipasvir ↑, darunavir ↔[a]	Daclatasvir ↑; darunavir ↔	Paritaprevir ↓/↑; darunavir ↓
Ritonavir-boosted lopinavir	No data	No data	No data[a]	Daclatasvir ↑; lopinavir ↔	Paritaprevir ↑; lopinavir ↔
Ritonavir-boosted tipranavir	No data	No data	No data	No data	No data
Efavirenz	Simeprevir ↓; efavirenz ↔	Sofosbuvir ↔; efavirenz ↔	Ledipasvir ↓; efavirenz ↓[a]	Daclatasvir ↓[b]	No pharmacokinetic data[c]
Rilpivirine	Simeprevir ↔; rilpivirine ↔	Sofosbuvir ↔; rilpivirine ↔	Ledipasvir ↔; rilpivirine ↔	No data	Paritaprevir ↑; rilpivirine ↑
Etravirine	No data	No data	No data	Daclatasvir ↓[b]	No data
Raltegravir	Simeprevir ↔; raltegravir ↔	Sofosbuvir ↔; raltegravir ↔	Ledipasvir ↔; raltegravir ↔	No data	PrOD↔; ↑ raltegravir
Cobicistat-boosted elvitegravir	No data	Cobicistat ↑[a]; sofosbuvir ↑	Cobicistat ↑; ledipasvir ↑[a]	No data	No data
Dolutegravir	No data	No data	Ledipasvir ↔; dolutegravir ↔	Daclatasvir ↔; dolutegravir ↑	Paritaprevir ↓; dolutegravir ↑
Maraviroc	No data	No data	No data	No data	No data
Tenofovir disoproxil fumarate	Simeprevir ↔; tenofovir disoproxil fumarate ↔	Sofosbuvir ↔; tenofovir disoproxil fumarate ↔	Ledipasvir ↔; tenofovir disoproxil fumarate ↑	Daclatasvir ↔; tenofovir disoproxil fumarate ↔	PrOD ↔; tenofovir disoproxil fumarate ↔

AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

AASLD

IDSA
Infectious Diseases Society of America

Recommended regimens for HIV/HCV-coinfected individuals.

HIV/HCV-coinfected persons should be treated and retreated the same as persons without HIV infection, after recognizing and managing interactions with antiretroviral medications (see Initial Treatment of HCV Infection and Retreatment of Persons in Whom Prior Therapy Has Failed sections).

Rating: Class I, Level B

Antiretroviral drug switches, when needed, should be done in collaboration with the HIV practitioner. For HIV antiretroviral and HCV direct-acting antiviral combinations not addressed below, expert consultation is recommended.

Rating: Class I, Level A

The following regimens are NOT recommended for treatment-naive or -experienced HIV/HCV-coinfected patients.

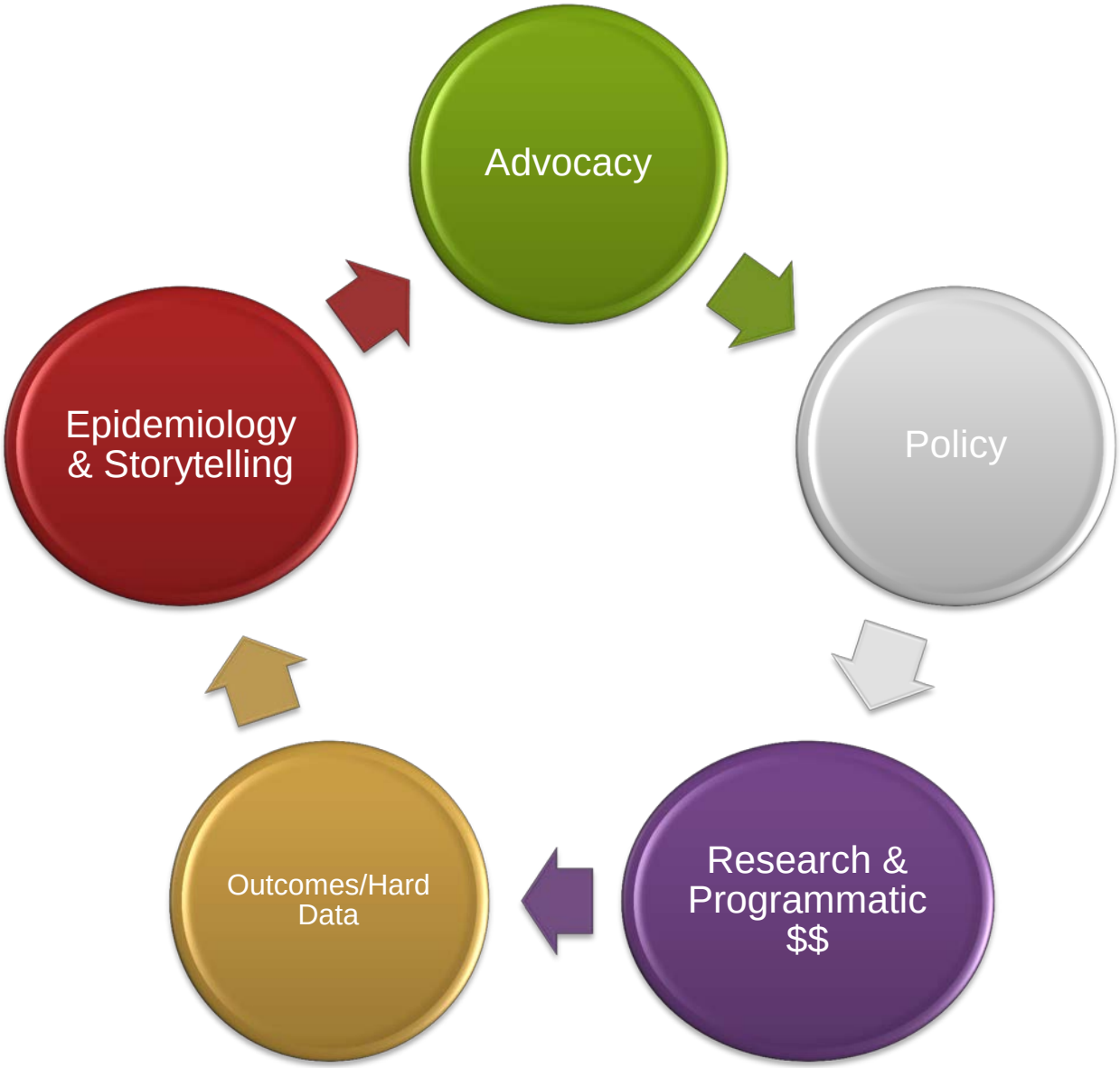
- **Treatment courses shorter than 12 weeks, such as the use of 8 weeks of ledipasvir/sofosbuvir**

  Rating: Class IIb, Level C

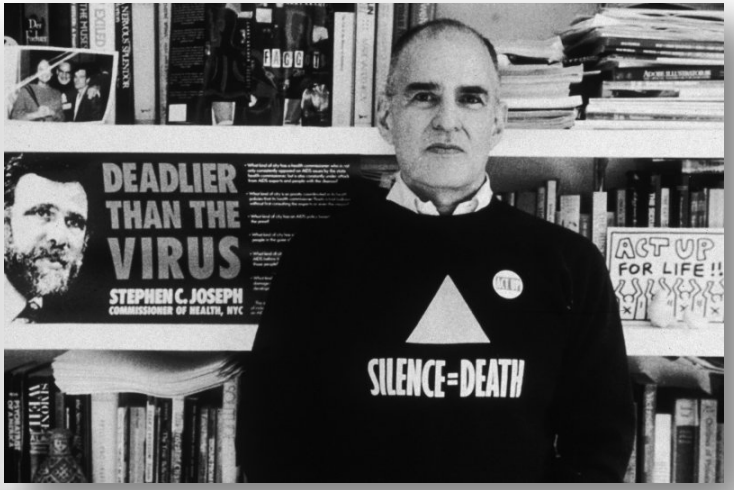
Overview

- The problem of hepatitis C in HIV patients
- Recently approved directly acting agents with data for HIV patients
- Practical Concerns
- **The Lessons of Advocacy**

How Did $15-20,000/yr Become the Law?

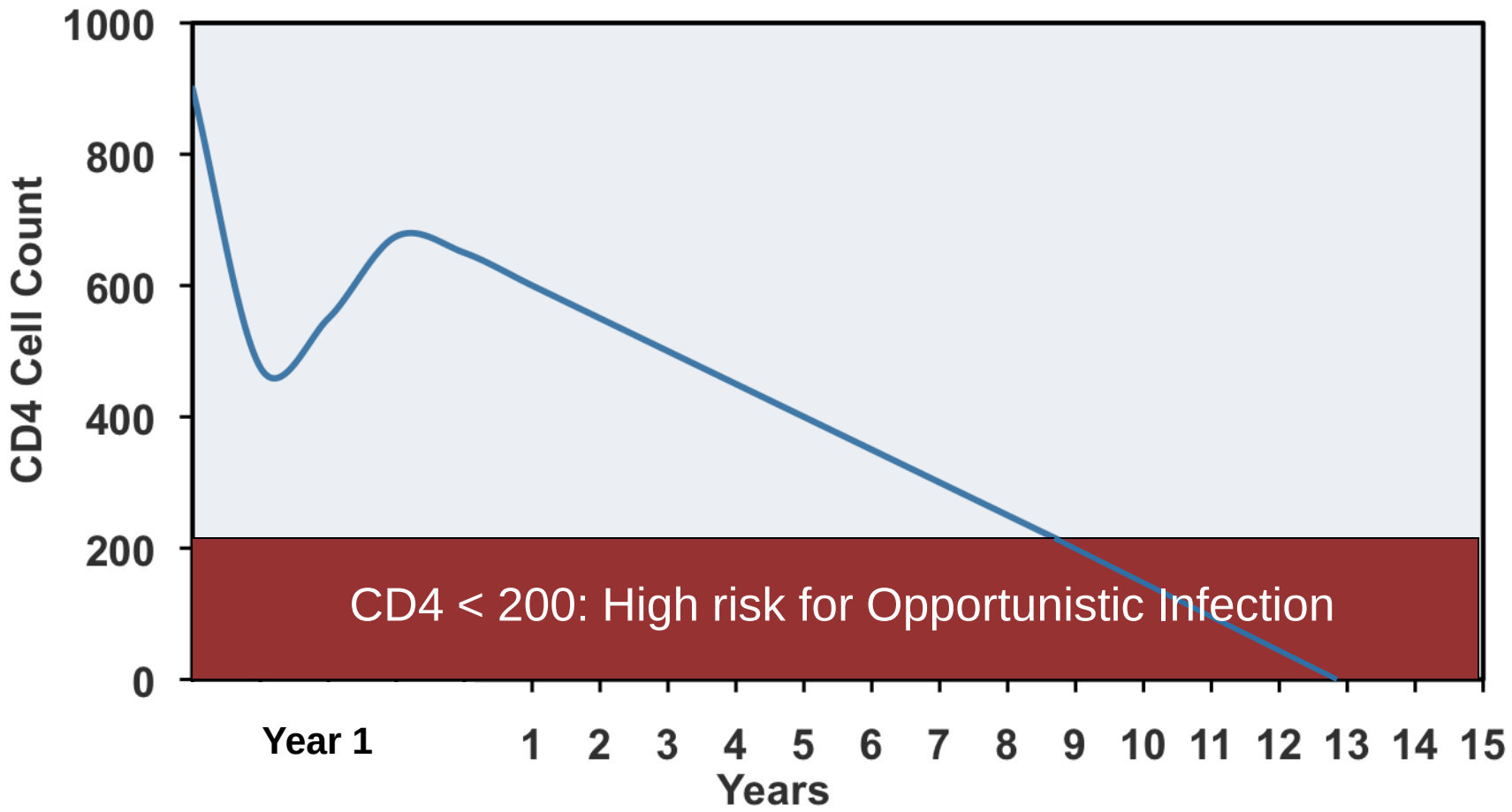


The Rise of HIV Activism and Advocacy

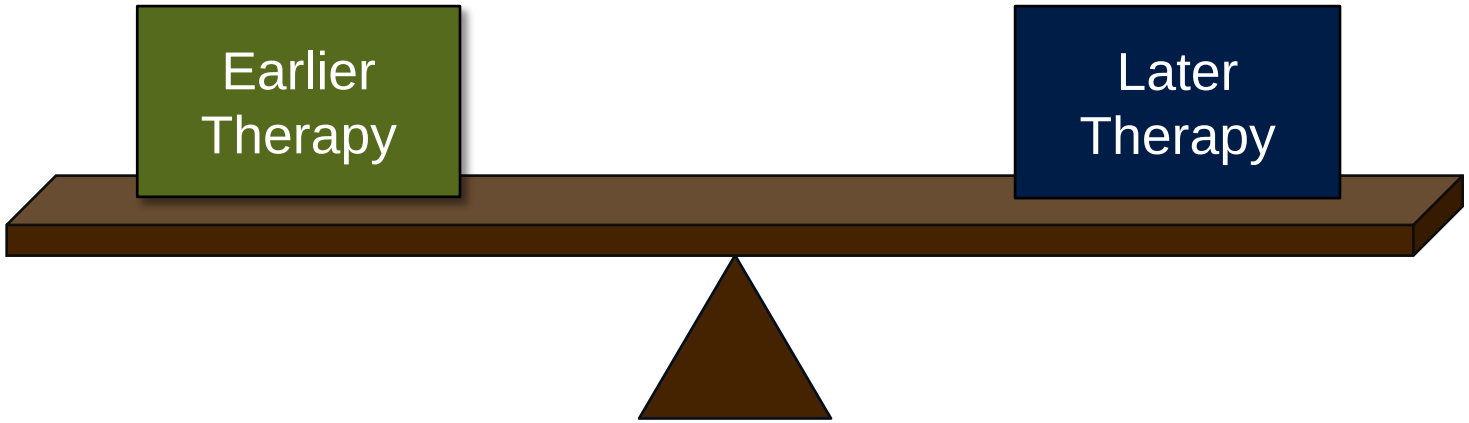


AIDS Memorial Quilt

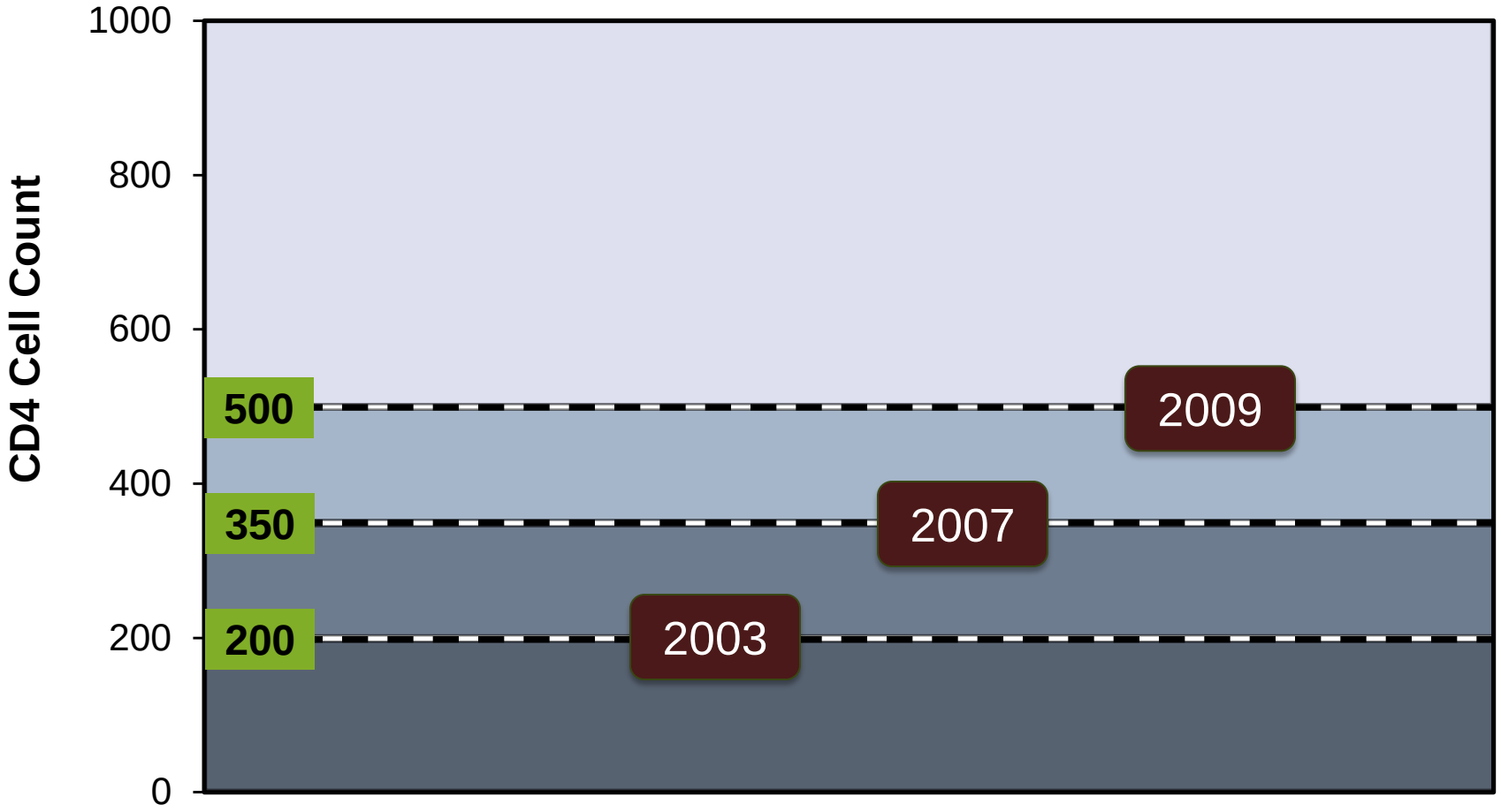
Natural History of Untreated HIV Infection



Initiating Therapy in Treatment-Naïve Patients

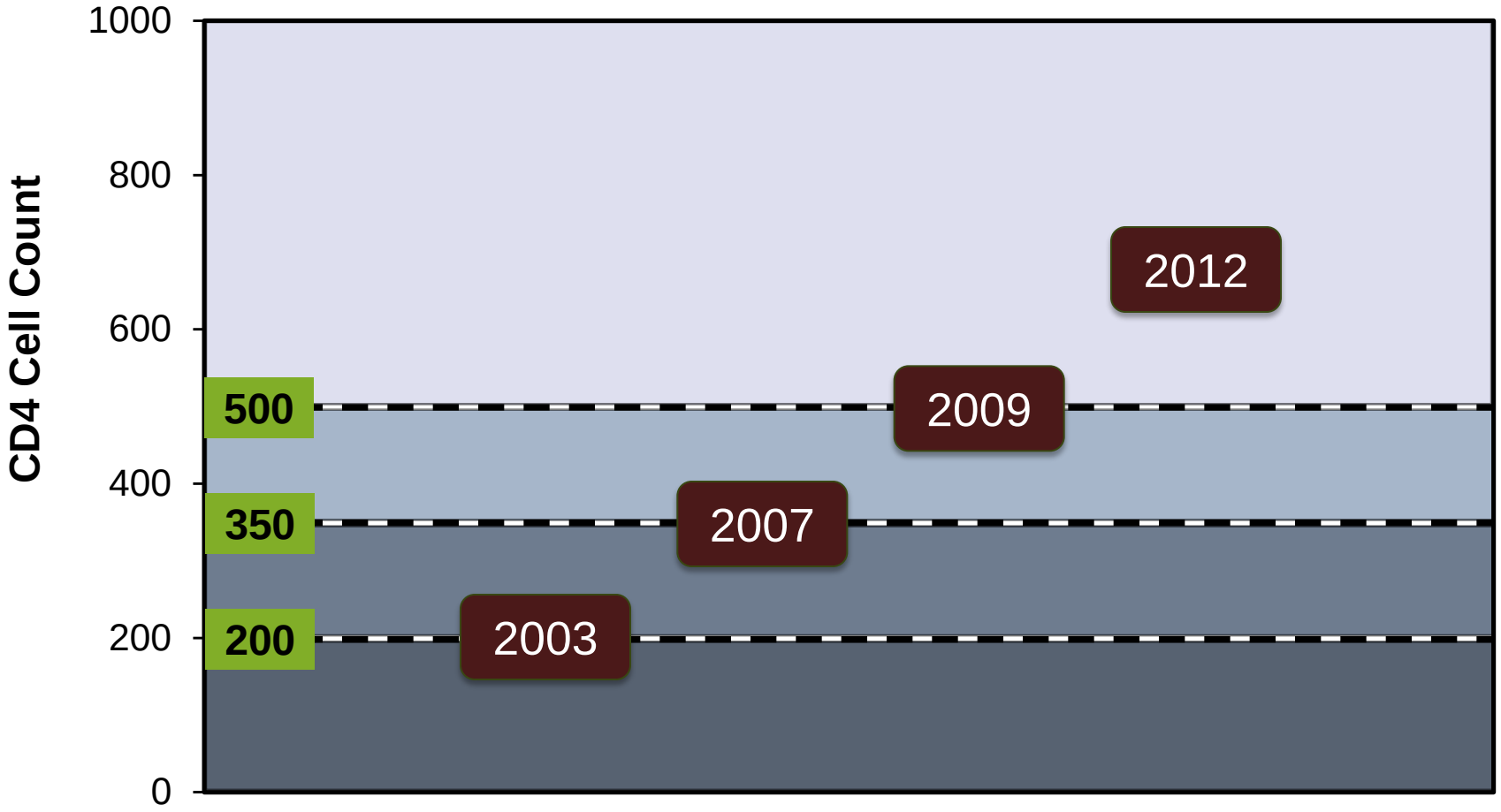


Initiating Antiretroviral Therapy in Treatment-Naïve Patients
Change in CD4 Threshold in DHHS Guidelines



DHHS Antiretroviral Therapy Guidelines. (aidsinfo.nih.gov)

Initiating Antiretroviral Therapy in Treatment-Naïve Patients
Change in CD4 Threshold in DHHS Guidelines

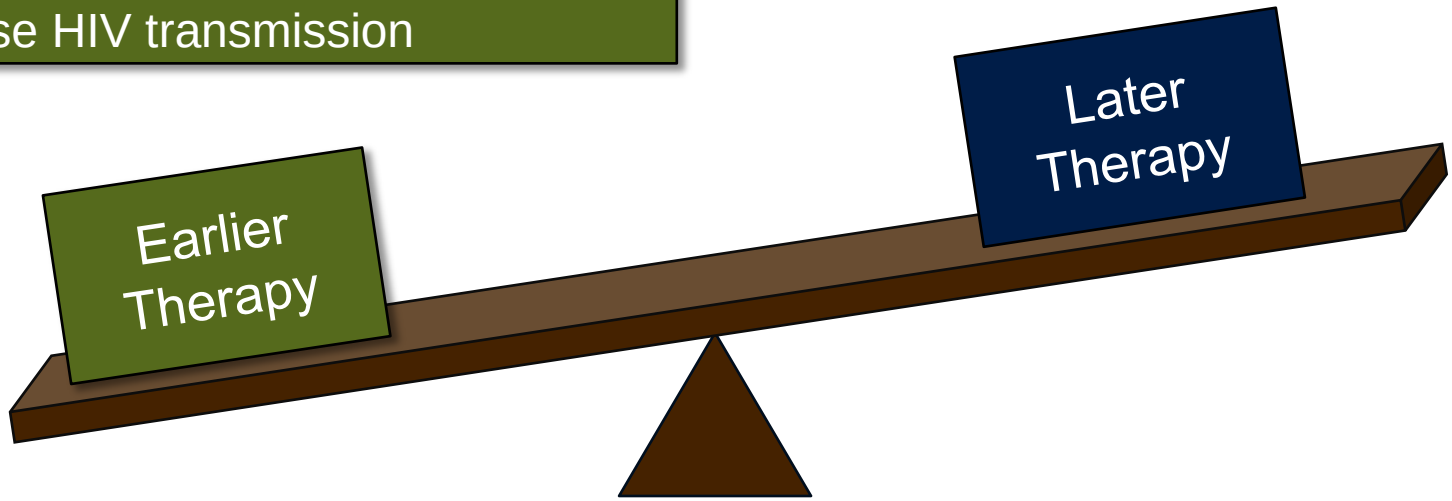


DHHS Antiretroviral Therapy Guidelines. (www.aidsinfo.nih.gov)

DHHS Antiretroviral Therapy Guidelines: March 2012
Factors Affecting Decision on When to Initiate Therapy

- More effective regimens
- More convenient regimens
- Better tolerated therapy
- Less long-term toxicity
- Better immune recovery
- Lower rates of resistance
- More treatment options
- Concerns for uncontrolled viremia
- Decrease HIV transmission

- Lack of RCT data supporting early Rx
- Potential drug toxicity
- Drug and monitoring cost
- Potential negative impact on QOL



START Trial: Benefits of ART in ALL HIV-Infected Patients Regardless of CD4 Count?

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 27, 2015 VOL. 373 NO. 9

Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection

The INSIGHT START Study Group*

ABSTRACT

BACKGROUND

Data from randomized trials are lacking on the benefits and risks of initiating antiretroviral therapy in patients with asymptomatic human immunodeficiency virus (HIV) infection who have a CD4+ count of more than 350 cells per cubic millimeter.

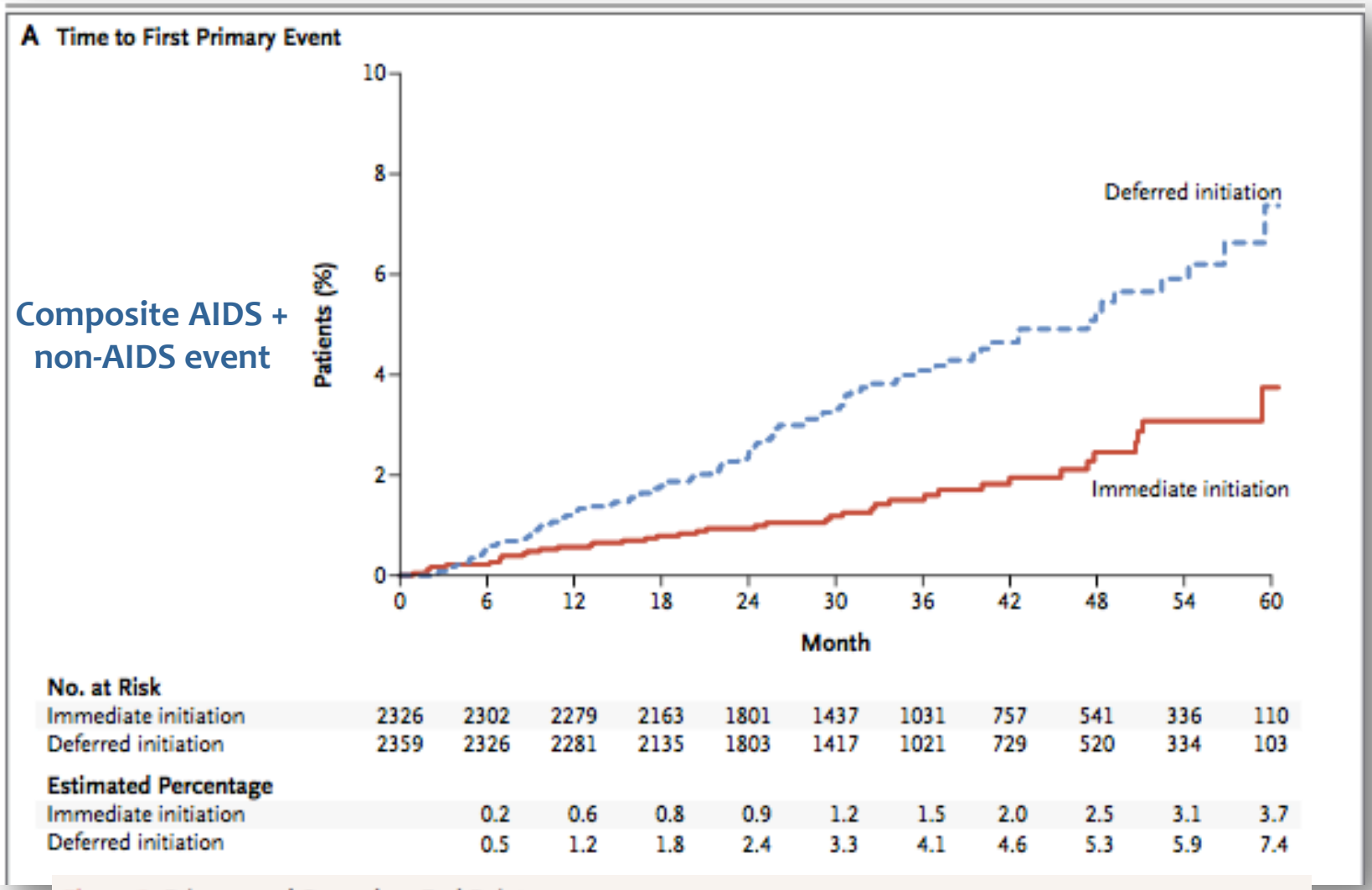
METHODS

We randomly assigned HIV-positive adults who had a CD4+ count of more than 500 cells per cubic millimeter to start antiretroviral therapy immediately (immediate-initiation group) or to defer it until the CD4+ count decreased to 350 cells per cubic millimeter or until the development of the acquired immunodeficiency syndrome (AIDS) or another condition that dictated the use of antiretroviral therapy (deferred-initiation group). The primary composite end point was any serious AIDS-related event, serious non–AIDS-related event, or death from any cause.

RESULTS

The members of the writing group (Jens D. Lundgren, M.D. [cochair], Abdel G. Babiker, Ph.D. [cochair], Fred Gordin, M.D. [cochair], Sean Emery, Ph.D., Birgit Grund, Ph.D., Shweta Sharma, M.S., Anchalee Avihingsanon, M.D., David A. Cooper, M.D., Gerd Fätkenheuer, M.D., Josep M. Llibre, M.D., Jean-Michel Molina, M.D., Paula Munderi, M.D., Mauro Schechter, M.D., Robin Wood, M.D., Karin L. Klingman, M.D., Simon Collins, H. Clifford Lane, M.D., Andrew N. Phillips, Ph.D., and James D. Neaton, Ph.D. [INSIGHT PI]) of the INSIGHT START Study Group assume responsibility for the overall content and integrity of this article. The affiliations of the members of the writing group are listed in the Ap-

START Trial: Benefits of ART in ALL HIV-Infected Patients Regardless of CD4 Count?



No. at Risk											
Immediate initiation	2326	2302	2279	2163	1801	1437	1031	757	541	336	110
Deferred initiation	2359	2326	2281	2135	1803	1417	1021	729	520	334	103
Estimated Percentage											
Immediate initiation		0.2	0.6	0.8	0.9	1.2	1.5	2.0	2.5	3.1	3.7
Deferred initiation		0.5	1.2	1.8	2.4	3.3	4.1	4.6	5.3	5.9	7.4

Figure 2. Primary and Secondary End Points.

Shown are Kaplan–Meier estimates of the cumulative percentages of patients with the composite primary end point (a serious AIDS-related or serious non–AIDS-related event, including death) in the two study groups (Panel A).

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wp OPINIONS

The global AIDS response can help in fighting hepatitis C

By Paul Farmer, Published: February 12

Paul Farmer is a professor at Harvard University and an infectious disease physician with the Brigham and Women's Hospital in Boston. He co-founded Partners in Health.

"The idea that some lives matter less is the root of all that's wrong with the world."

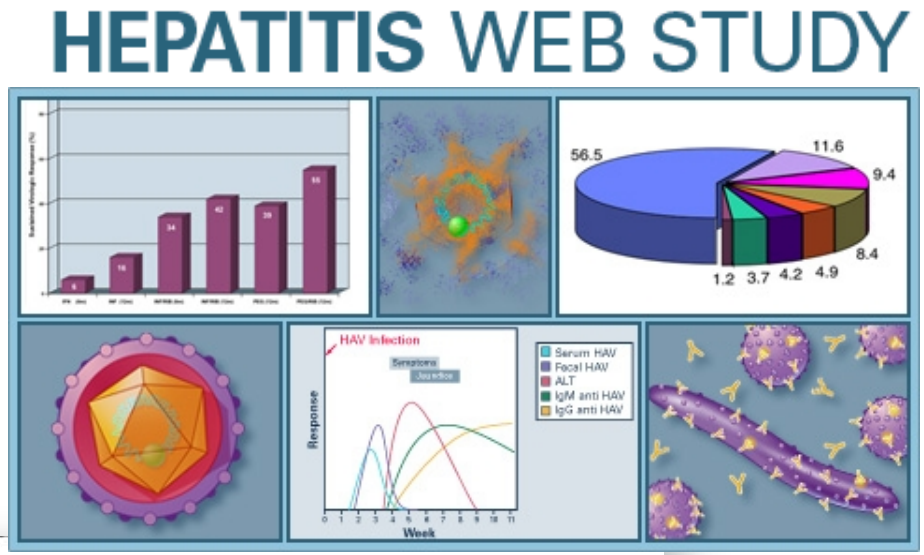
—DR. PAUL FARMER

Chief Strategist & Co-founder

Partners In Health

Web Resources

- www.hcvguidelines.org
- www.hepatitisc.uw.edu
- www.nwaetcecho.org
- www.hepwebstudy.org
- www.hivwebstudy.org



Thank you!

Questions?

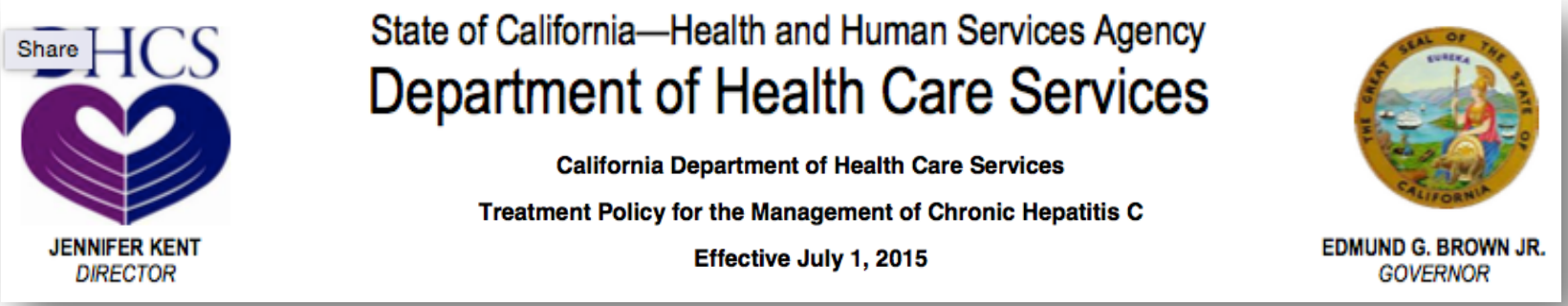
Additional Slides

Mounting Evidence supporting Earlier HAART

Study	Type	Setting	Main Findings
CIPRA HT 001	RCT	Haiti	Deferring ART until CD4<200 associated with higher mortality than starting when CD4 between 200 and 350
SMART substudy	RCT	Europe, Australia	Deferring ART until CD4<250 associated with higher mortality than starting when CD4 between 350 and 250
ART-CC	Obs	Europe, North America	Significant increase in risk of AIDS and death when therapy was delayed until patients CD4+ counts fell below 350 cells/mm^3 compared to earlier treatment.
NA-ACCORD	Obs	North America	69% lower mortality in those who initiated in 350-500 range than those who deferred; 94% lower mortality in those who initiated at CD4 > 500 than in those who deferred
HPTN 052	RCT	Africa, US, Asia, S. America	96% decrease in transmission of HIV in serodiscordant couples when one partner on ART; 41% decrease in AIDS-related events (extra-pulmonary TB) for those on ART

CID. 2009 Apr 15;48(8):1138-51; 16th CROI, 2009 Abs 72LB; JID 2008;197:1133–1144; NEJM 2009;360:1815

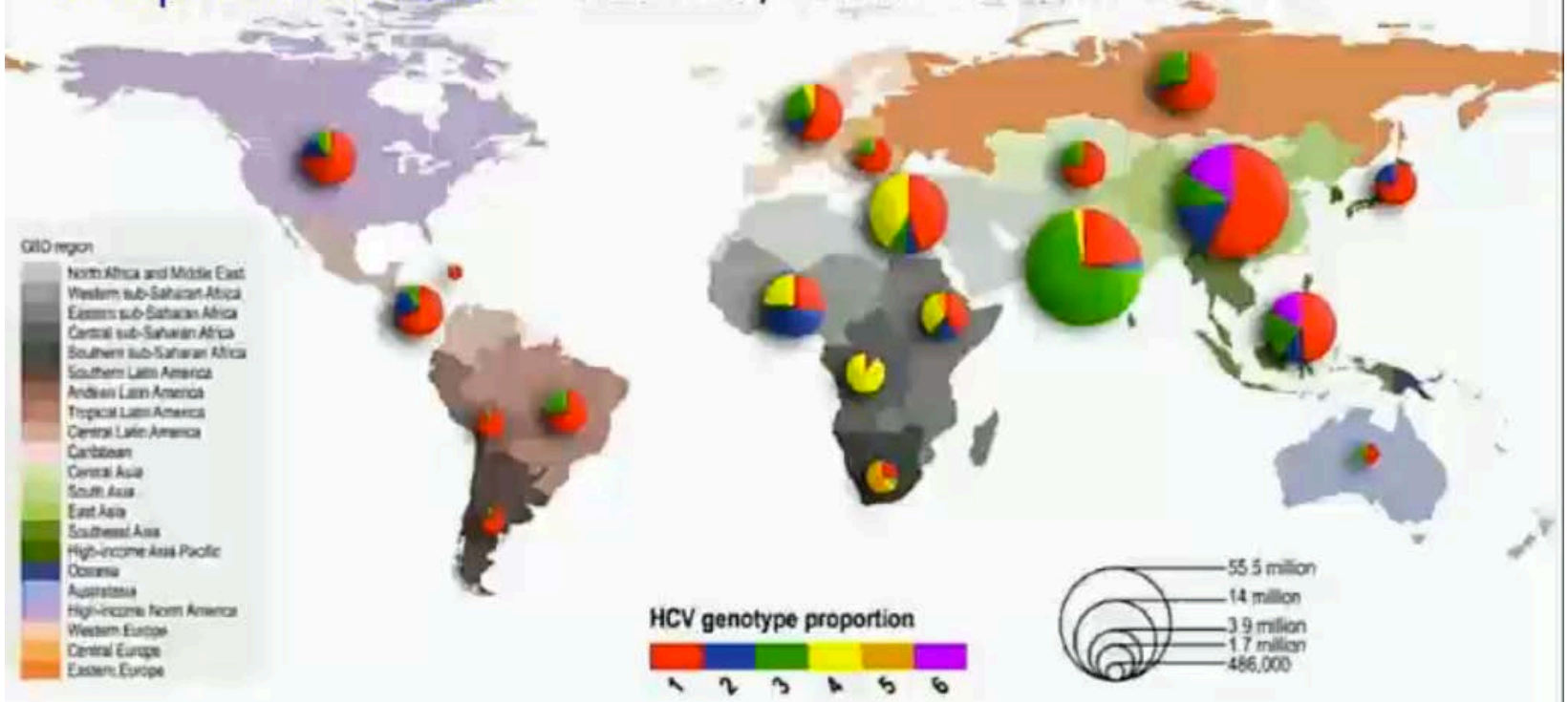
California Medi-cal HCV Treatment Policy



1. Treatment considerations and choice of regimen for hepatitis C virus infected patients:
   A. Please refer to AASLD guidelines (hcvguidelines.org) for recommended treatment regimens and durations.
2. Identifying treatment candidates:
   A. Disease Prognosis and Severity—Any of the following clinical states identify candidates for treatment:
      i. Evidence of Stage 2 or greater hepatic fibrosis/cirrhosis including one of the following: Liver biopsy confirming a METAVIR score F2 or greater; OR Transient elastography (Fibroscan®) score greater than or equal to 7.5 kPa; OR FibroSure® score of greater than or equal to 0.48; OR APRI score greater than 0.7 OR FIB-4 greater than 3.25.
      ii. Evidence of extra-hepatic manifestation of hepatitis C virus, such as type 2 or 3 essential mixed cryoglobulinemia with end- organ manifestations (e.g. vasculitis), or kidney disease (e.g. proteinuria, nephrotic syndrome or membranoproliferative glomerulonephritis).
      iii. Persons with hepatocellular carcinoma with a life expectancy of greater than 12 months
      iv. Pre- and post-liver transplant, or other solid organ transplant
      v. HIV-1 co-infection
      vi. Hepatitis B co-infection
      vii. Other coexistent liver disease (e.g. nonalcoholic steatohepatitis)
      viii. Type 2 diabetes mellitus (insulin resistant)
      ix. Porphyria cutanea tarda
      x. Debilitating fatigue impacting quality of life (e.g., secondary to extra-hepatic manifestations and/or liver disease)
      xi. Men who have sex with men with high-risk sexual practices
      xii. Active injection drug users
      xiii. Persons on long-term hemodialysis
      xiv. Women of childbearing age who wish to get pregnant.
      xv. HCV-infected health care workers who perform exposure-prone procedures

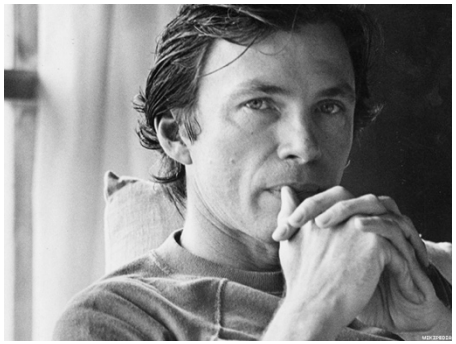
Global HCV Eradication: the next frontier

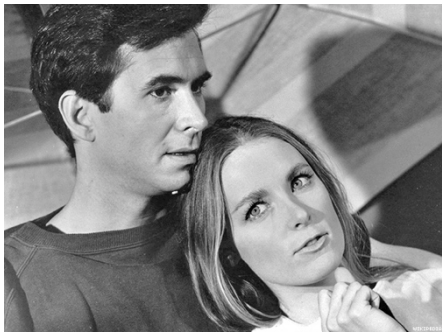
Worldwide prevalence of each HCV genotype by GBD region. Size of pie charts is proportional to the number of seroprevalent cases estimated by Hanafiah et al 2014: Messina 2015



HCV genotype 1 (83.4 million cases: 46.2%)- one-third of which are in East Asia. Genotype 3 (54.3 million: 30.1%); genotypes 2, 4, and 6 (22.8%); genotype 5 <1%. While genotypes 1 and 3 dominate in most countries irrespective of economic status, the largest proportions of genotypes 4 and 5 are in lower-income countries.

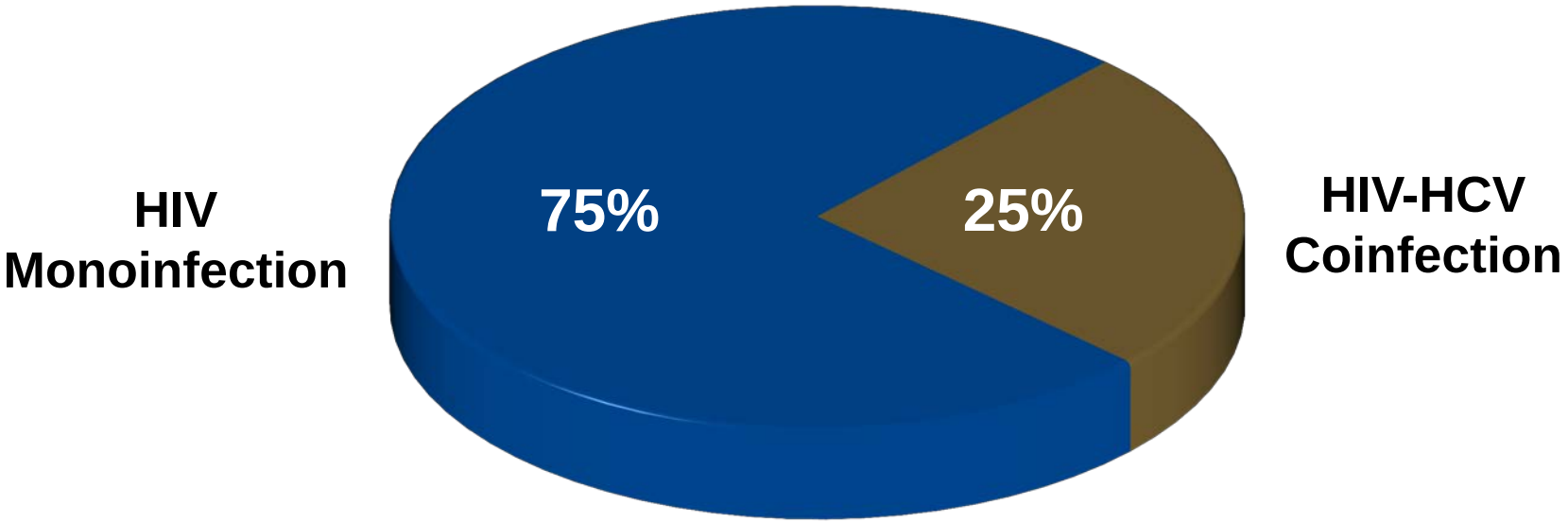
Famous People affected by AIDS





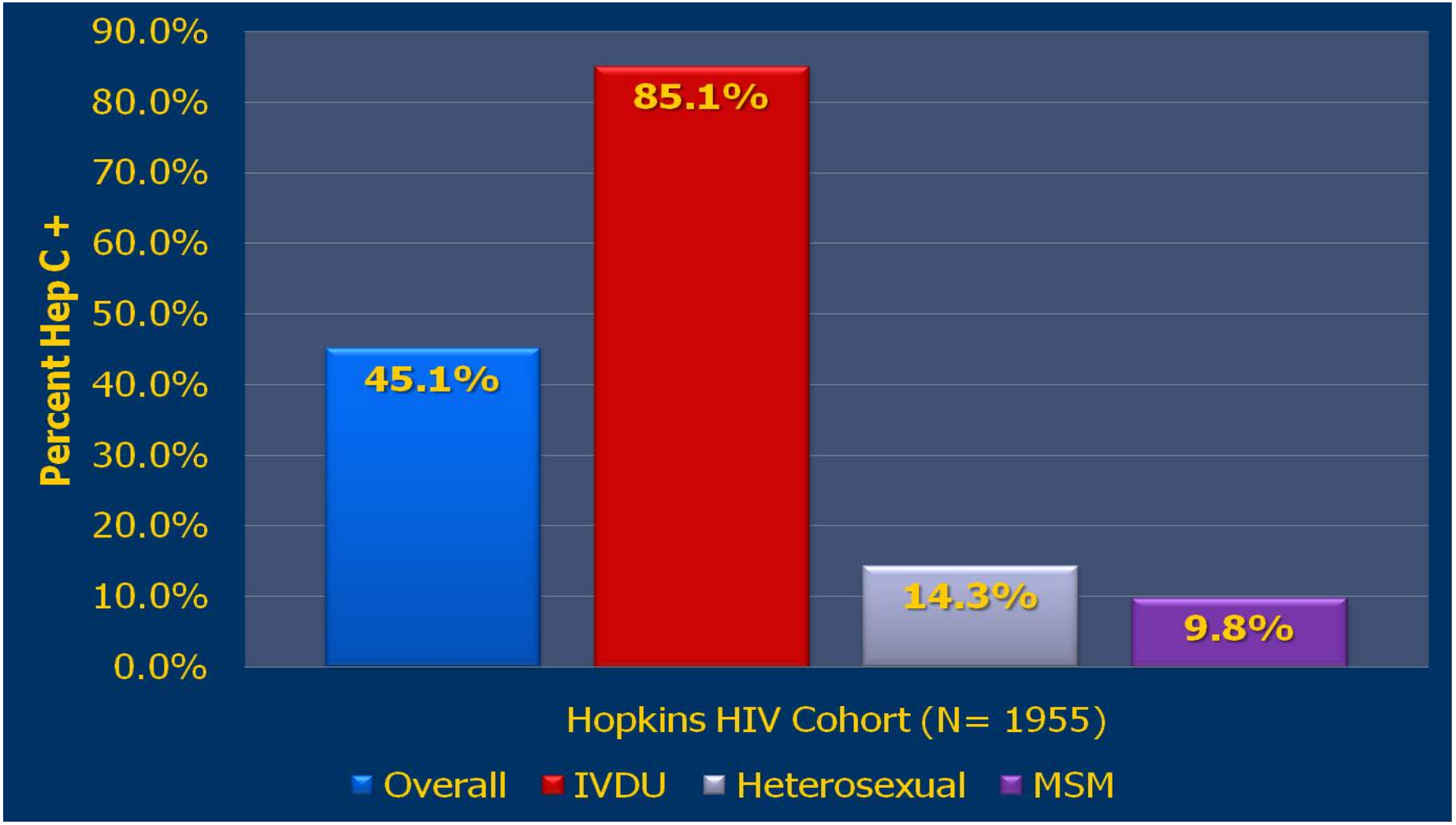
HCV-HIV Coinfection

HIV-Infected Persons in United States



Source: Sulkowski M, et al. Ann Intern Med. 2003;138:197-207; Alter MJ et al *J Hepatol* 2006:44:S6

Hepatitis C Prevalence in HIV+ Patients

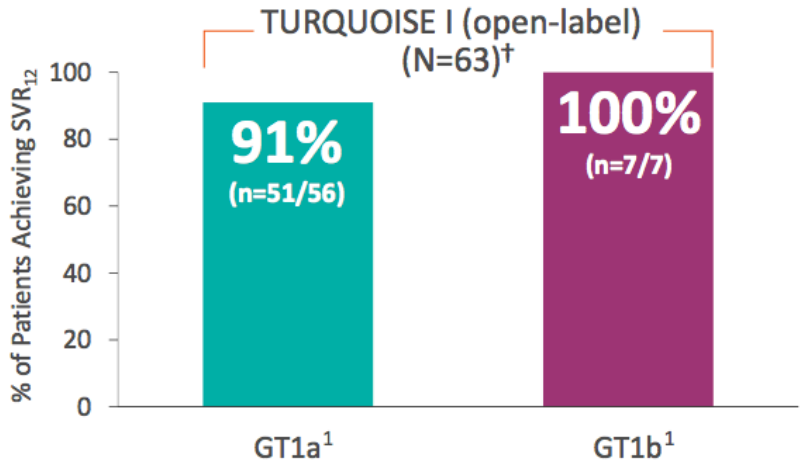


Sulkowski *et al Ann Int Med* 2003; 138: 197-207

OMB/PTV/r+DSV achieves high SVR12 in HIV/HCV

TURQUOISE I

High SVR_{12} Rates in Chronic GT1 HCV/HIV-1 Coinfected Patients



Recommended Regimen[1]	HCV/HIV-1 coinfected patients should follow the recommended regimen for VIEKIRA PAK +/- RBV in monoinfected patients.

1.6% **Post-treatment relapse[1]** (n=1/62)

1.6% **On-treatment virologic failure[1]** (n=1/63)

Of the 3 other patients who did not achieve SVR_{12}, 1 discontinued treatment, and 2 had evidence of HCV re-infection post treatment.[1]

SAFETY CONSIDERATIONS[1]

The ritonavir component of VIEKIRA PAK is an HIV-1 protease inhibitor and can select for HIV-1 protease inhibitor resistance. To reduce this risk, HCV/HIV-1 co-infected patients should also be on a suppressive antiretroviral drug regimen.

†12 of the 63 patients in TURQUOISE I trial also had compensated cirrhosis.[1]

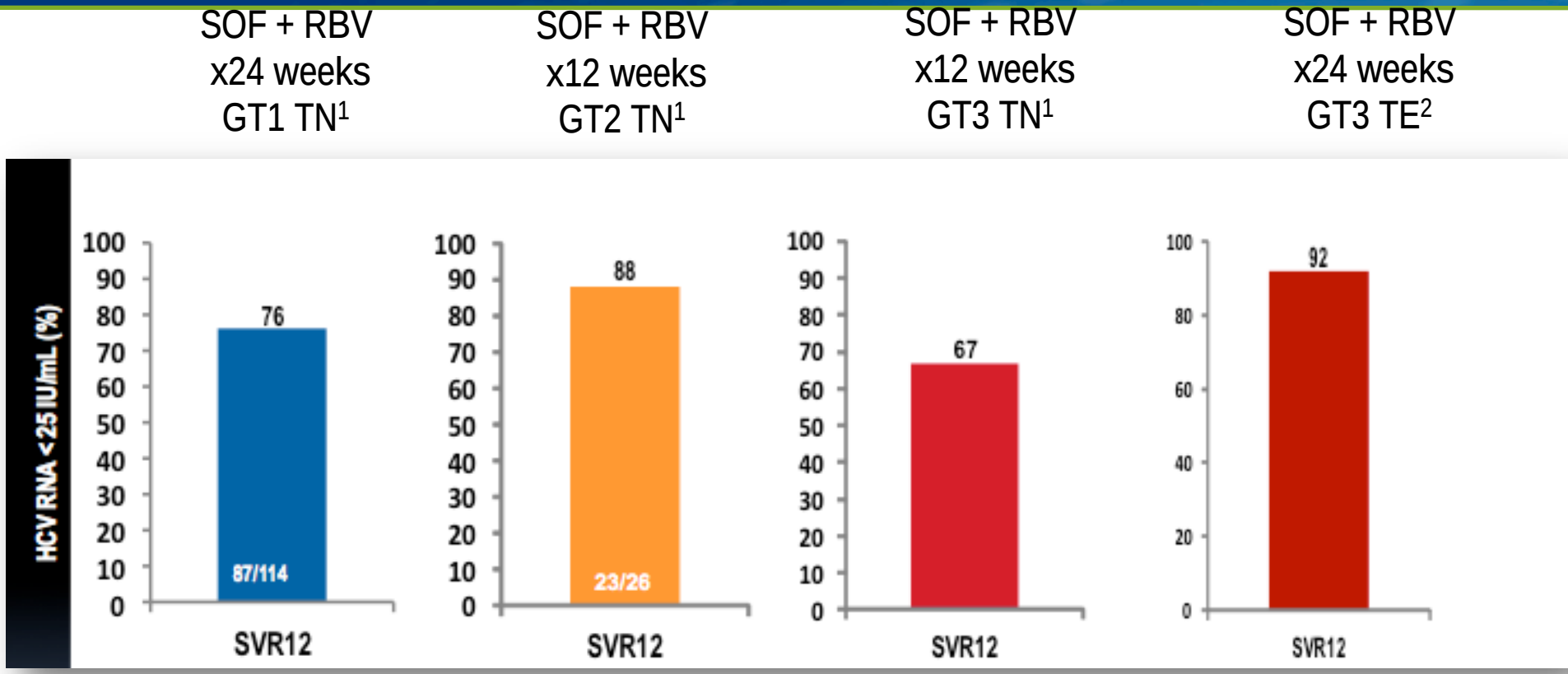
Please see Important Safety Information on slides 45-47, and accompanying full Prescribing Information.

viekira pak™
ombitasvir, paritaprevir and ritonavir tablets; dasabuvir tablets

1. VIEKIRA PAK [package insert] North Chicago, IL: AbbVie Inc.

046-1797533

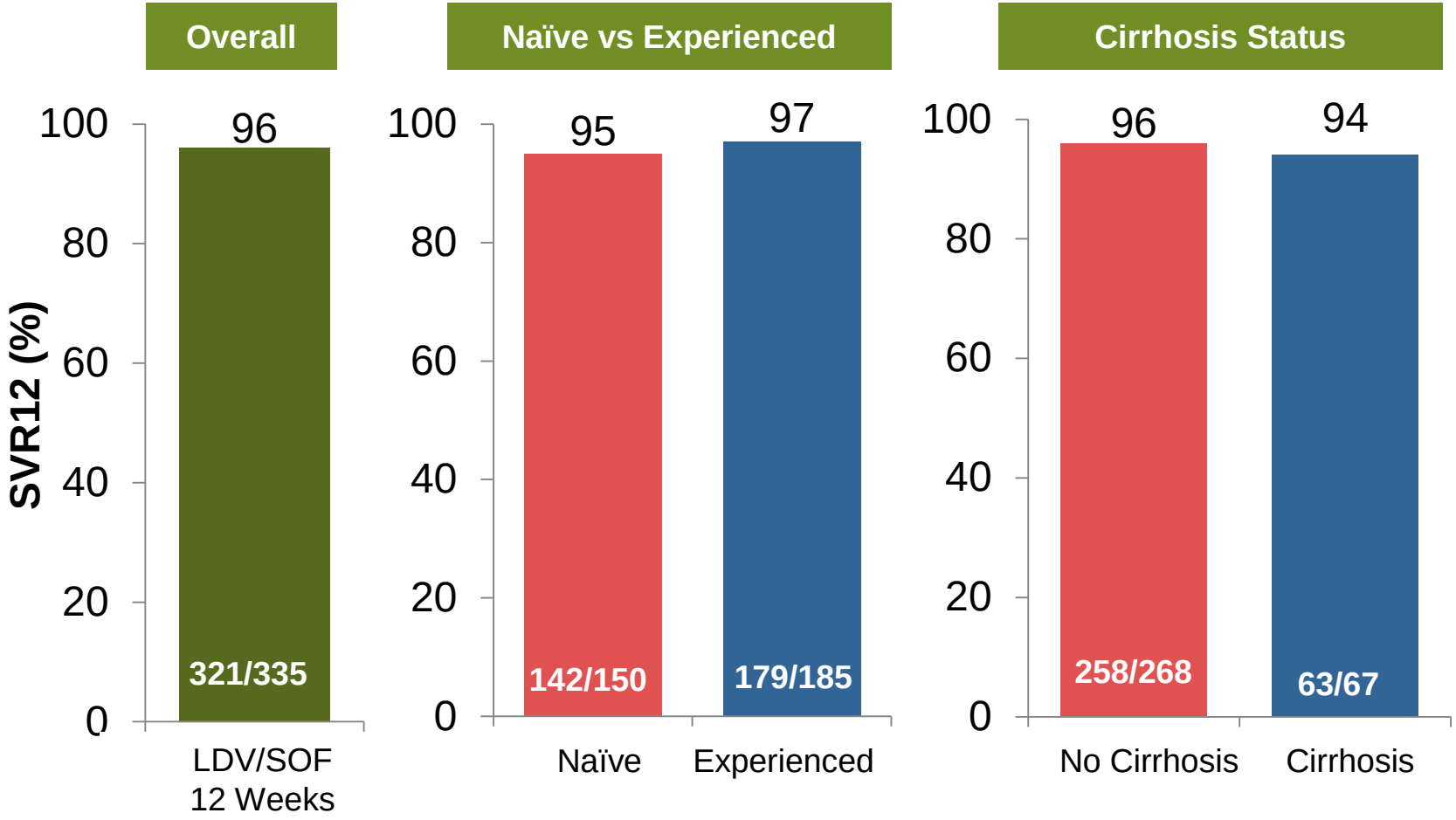
PHOTON-1: SOF+RBV in HIV/HCV GT-1-3



No HCV resistance (S282T) was observed in virologic failures via deep sequencing

1. Sulkowski MS, et al. AASLD 2013. Washington, DC. Oral #212;
2. SOVALDI™ [PI]. Gilead Sciences, Inc. Foster City, CA December 2013

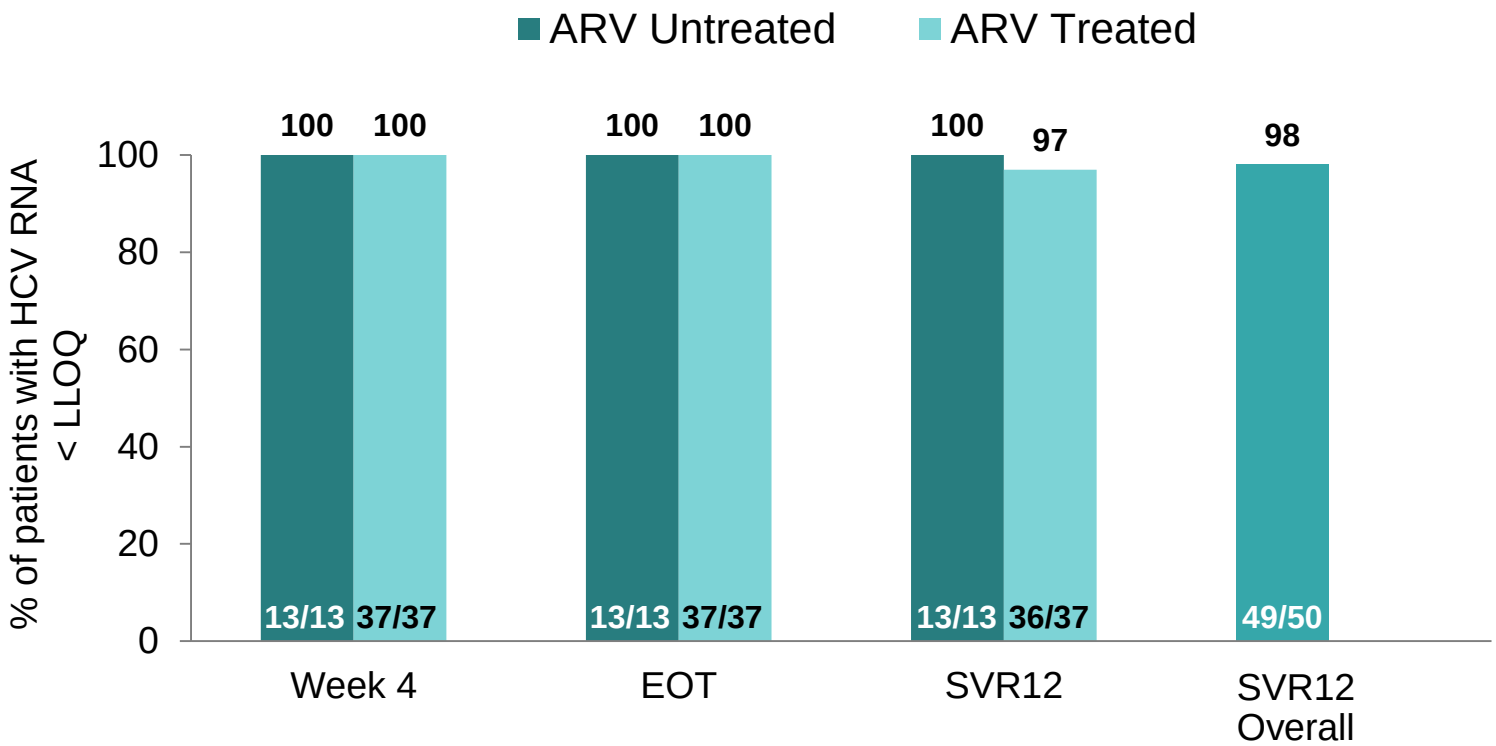
ION-4: SOF/LDV x 12 weeks in HIV/HCV GT1



- Among those who were treatment-experienced with cirrhosis, 98% (46/47) achieved an SVR12

Naggie et al, CROI 2015, Oral #LB-152

NIAID ERADICATE: LDV/SOF STR: SVR12



- LDV/SOF was safely administered in combination with several ARV regimens
  - Well tolerated with no discontinuations
  - No clinically significant CD4 T-cell count or HIV RNA changes, or renal toxicity were observed
  - No deaths, SAEs related to study drug, or D/C due to AE

Kottilil, AASLD, 2014, Oral #84