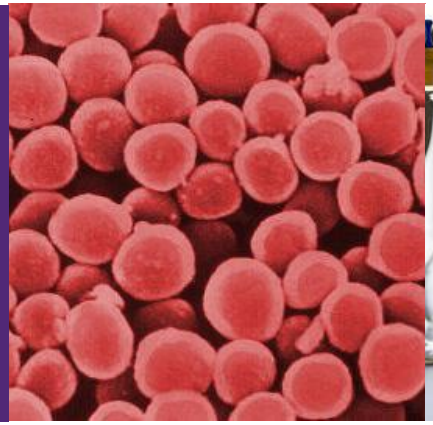
CUBIST



Cubist Pharmaceuticals

The Shape of Cures to Come™

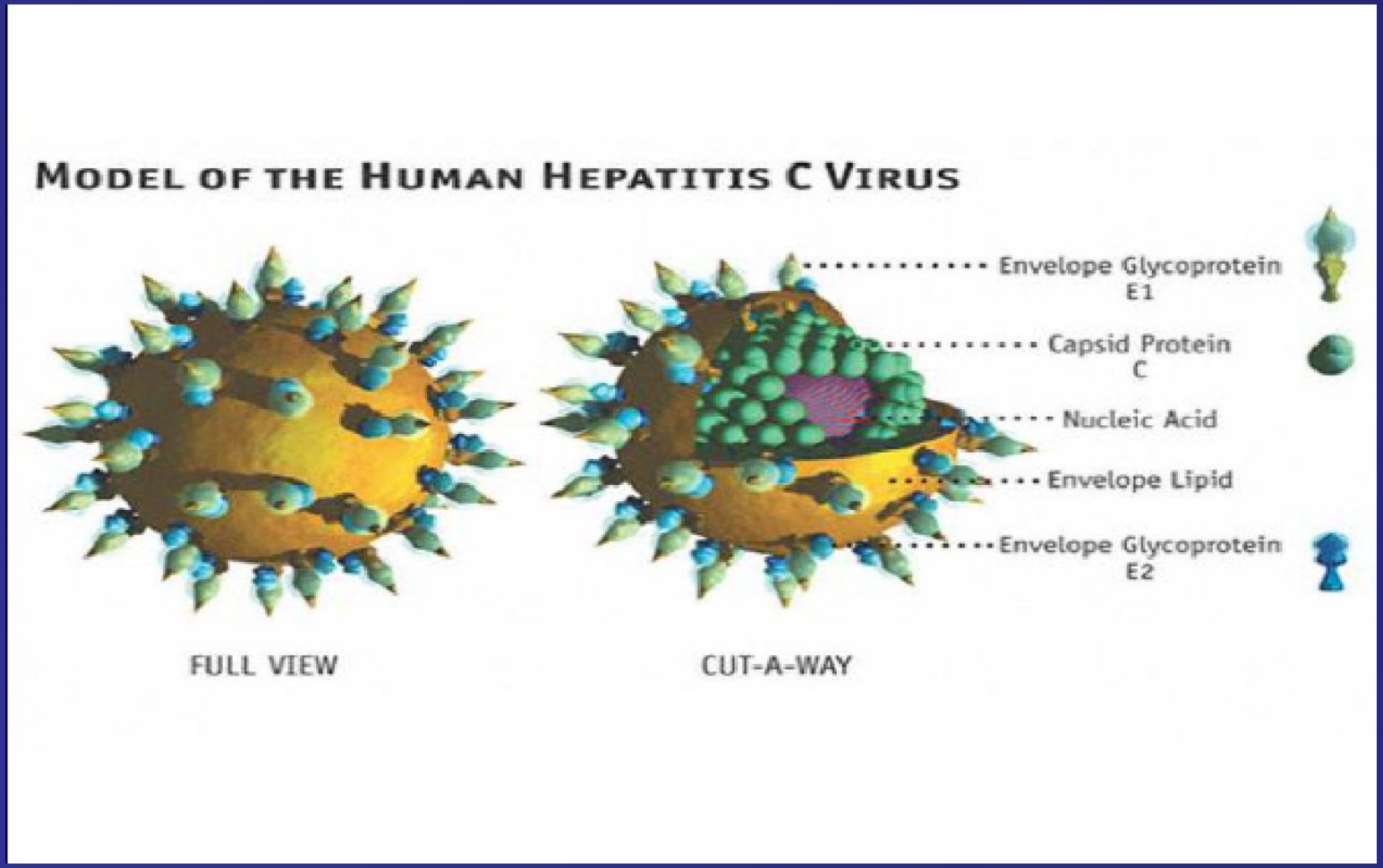
Pharmacological management of viruses in obese patients

Dr. Dimitar Tonev, Medical Director UKINORD

Disclosures

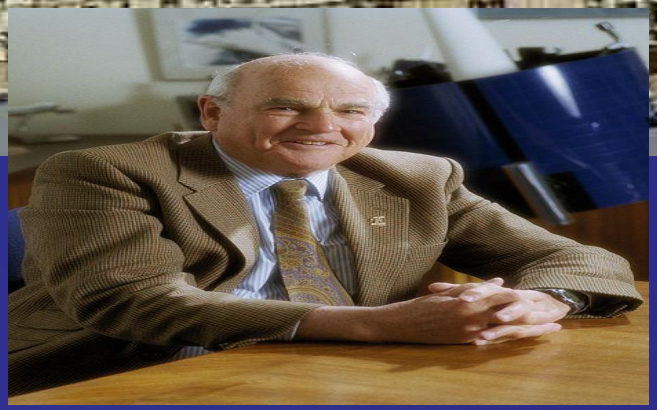
- The author is a pharmaceutical physician employed by Cubist and has also received "educational grants" from Janssen, Roche, Novartis and BMS
- Opinions expressed are these of the author and not necessarily Cubist or any of the other companies
- The presentation would not cover "off label" use but many of the treatment modalities are currently "off fashion" and have probably only a historical importance

HCV- a “clockwork orange”

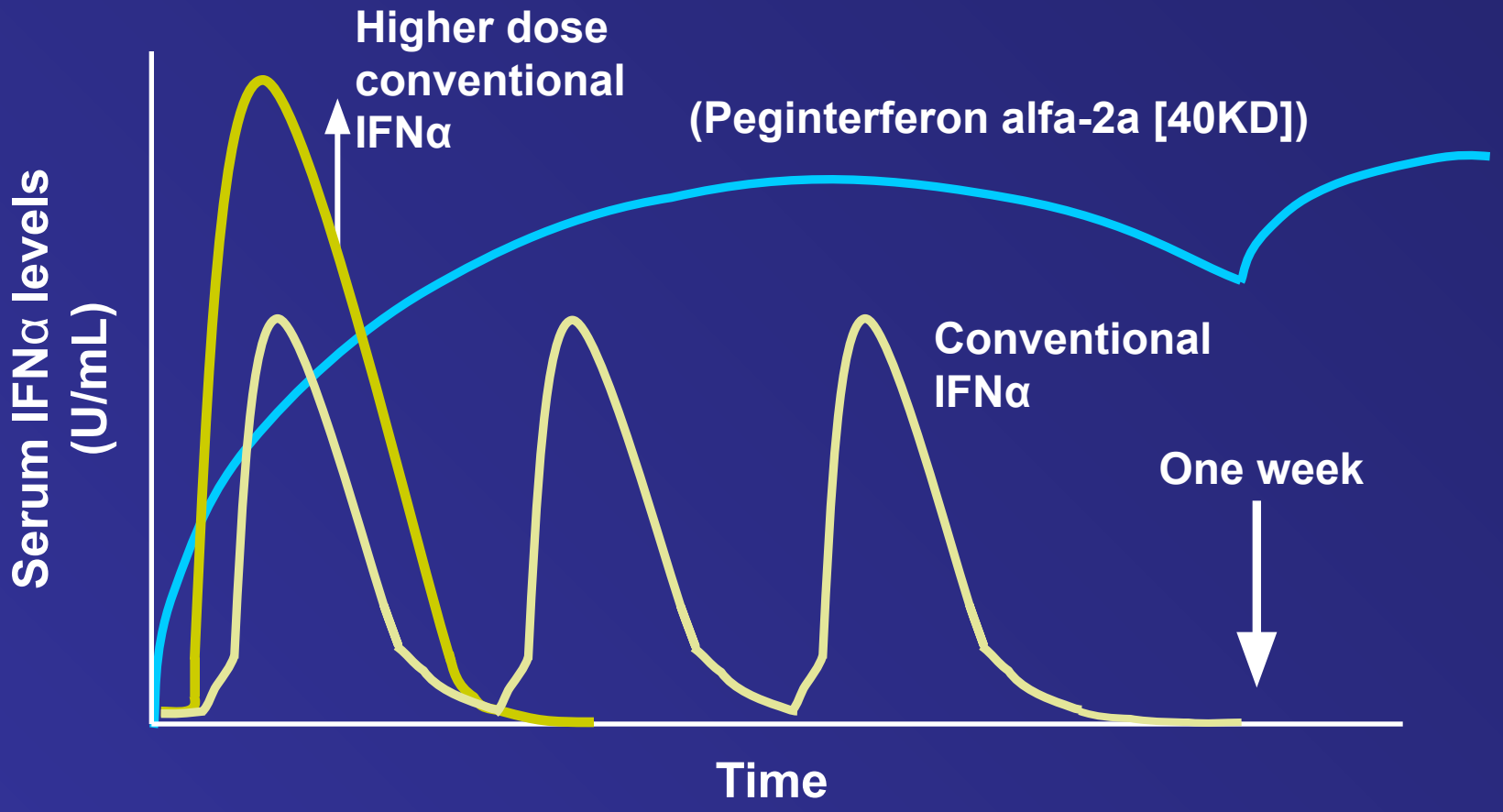


Adapted from Stanley Kubrick and Anthony Burges

UK science, viral hepatitis and rocket science (circa 1957)!?



Pegylation – a significant improvement over conventional interferons



1. Kozlowski A, et al. BioDrugs 2001; 15: 419
2. Perry C, Jarvis B. Drugs 2001; 61: 2263
3. Glue P, et al. Clin Pharmacol Ther 2000; 68: 556

Differences between the two currently available pegylated interferons

	Pegylated interferon alfa-2b (12KD)	Pegylated interferon alfa-2a (40KD)
Dosing	Weight based	Flat dose
PEG structure	Small, linear 12KD PEG	Large, branched 40KD PEG
Positional isomers	14	6
Protein bond	Unstable urethane bond	Stable amide bond

1. Bailon P, et al. Bioconjugate Chem 2001; 12: 195
2. Kozlowski A, et al. BioDrugs 2001; 15: 419
3. Wang Y-S, et al. Biochemistry 2000; 39: 10634
4. Youngster S, et al. Curr Pharm Des 2002; 8: 2139
5. Grace M, et al. J Interferon Cytokine Res 2001; 21: 1103

Summary of pharmacokinetics (PK)

Parameter	Peg-IFN α-2a [1]	Peg-IFN α-2b (12KD)
Attachment	40KD PEG	12KD PEG
Clearance	94 mL/h[1]	1540 mL/h[3,4]
Trough concentration	16 ng/mL[1]	0.32 ng/mL[3]
Peak:trough ratio	~2[1]	>10[5]
Volume of distribution	6–14 L[2]	63 L[5]
Terminal-half life	160 hours[1,2]	40 hours[3]

1. PEGASYS® US package insert
2. PEGASYS® EU SPC
3. PegIntron US package insert
4. Adapted from PegIntron US package insert for a 70 kg subject
5. Bruno R, et al. Antiviral Therapy 2004; 9: 491

Peginterferon alfa-2b + Ribavirin versus Interferon alfa-2b + Ribavirin

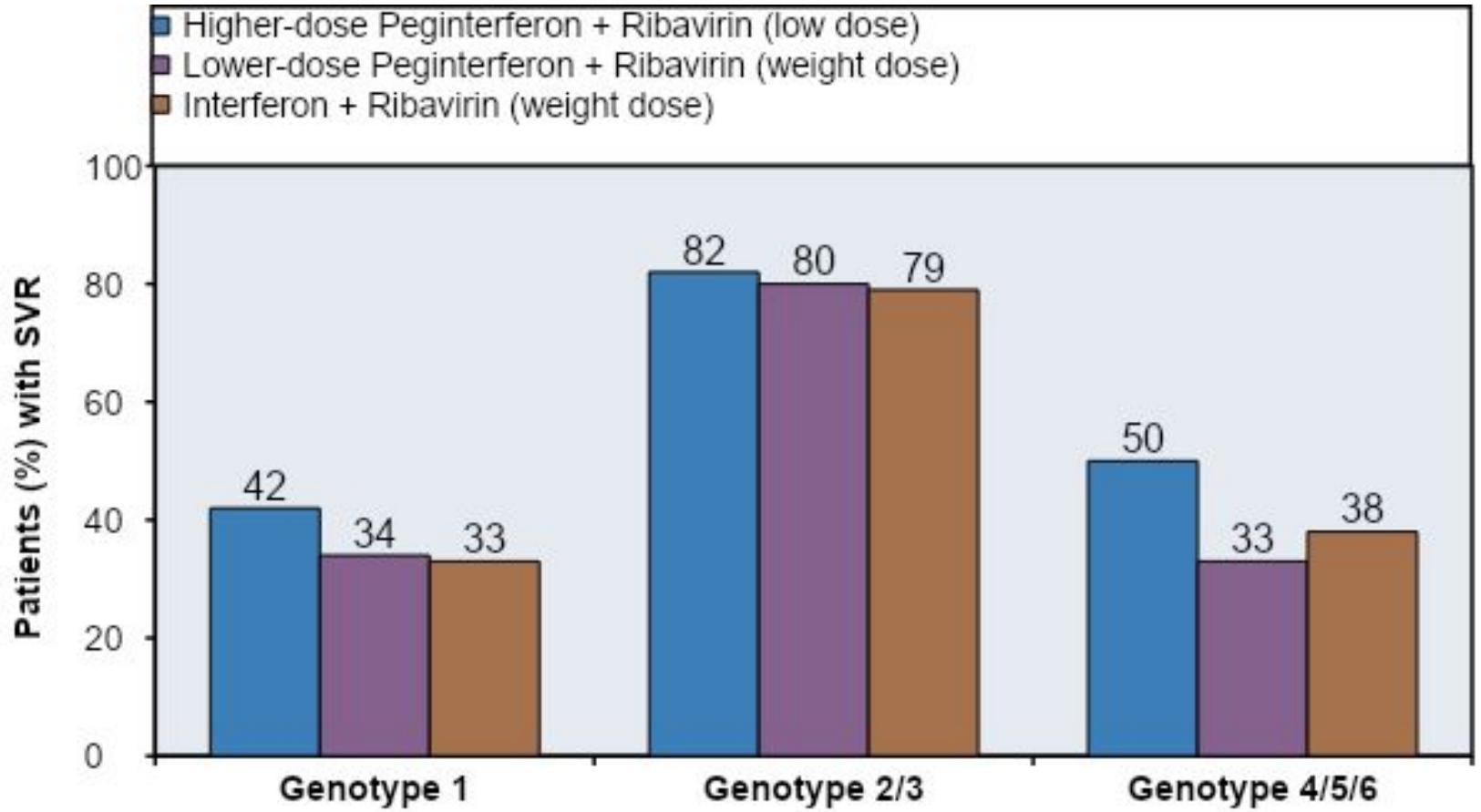
- **Study**
  - Open-label, randomized controlled trial
  - 62 sites in Europe, North America, & Argentina
- **Subjects**
  - N = 1530 with chronic hepatitis C
  - Treatment naïve
  - Genotype 1: 68%; Genotype 2 or 3: 29%; Genotype 4,5, or 6: 3%
  - Serum ALT >34 IU/L for women, >43 IU/L for men
- **Regimens**
  - Higher Dose Peginterferon alfa-2b: 1.5 µg/kg 1x/week + ribavirin 800 mg/day
  - Lower Dose Peginterferon alfa-2b: 1.5 µg/kg 1x/week x 4 weeks then 0.5 µg/kg 1x/week + ribavirin 1000-1200 mg/day*
  - Standard interferon alfa-2b: 3 million U 3x/week + ribavirin 1000-1200 mg/day*
- **Primary Endpoint (Sustained Virologic Response [SVR])**
  - SVR = Undetectable serum HCV RNA 24 weeks after 48-week treatments

*Ribavirin dosing: <75 kg: 1000 mg/day; ≥75 kg: 1200 mg/day

Manns MP, et. al. Lancet. 2001;358:958-65.

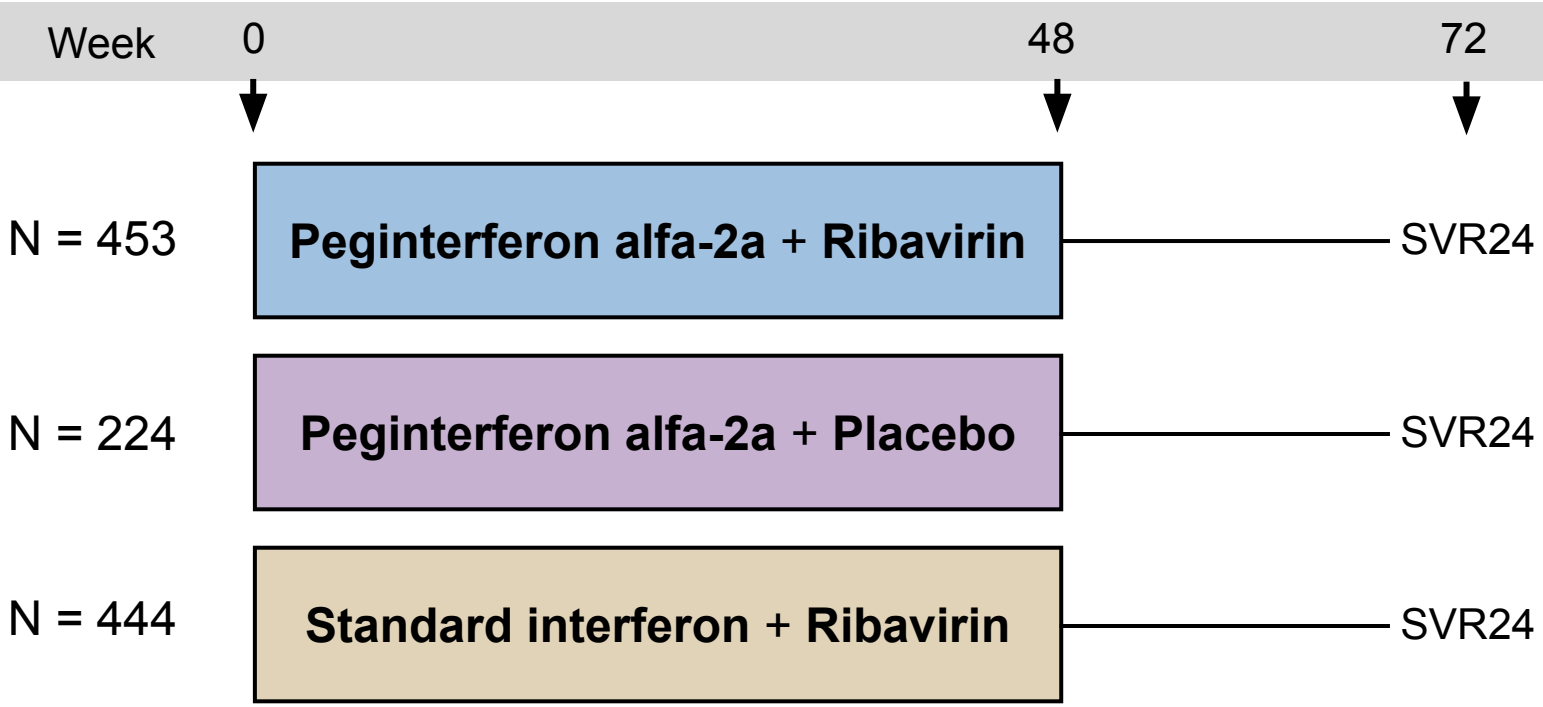
Peginterferon alfa-2b + Ribavirin versus Interferon alfa-2b + Ribavirin

SVR24, Based on Genotype



Manns MP, et. al. Lancet. 2001;358:958-65.

Peginterferon alfa-2a +/- Ribavirin for Chronic HCV



Drug Dosing

Peginterferon alfa-2a 180 µg 1x/week

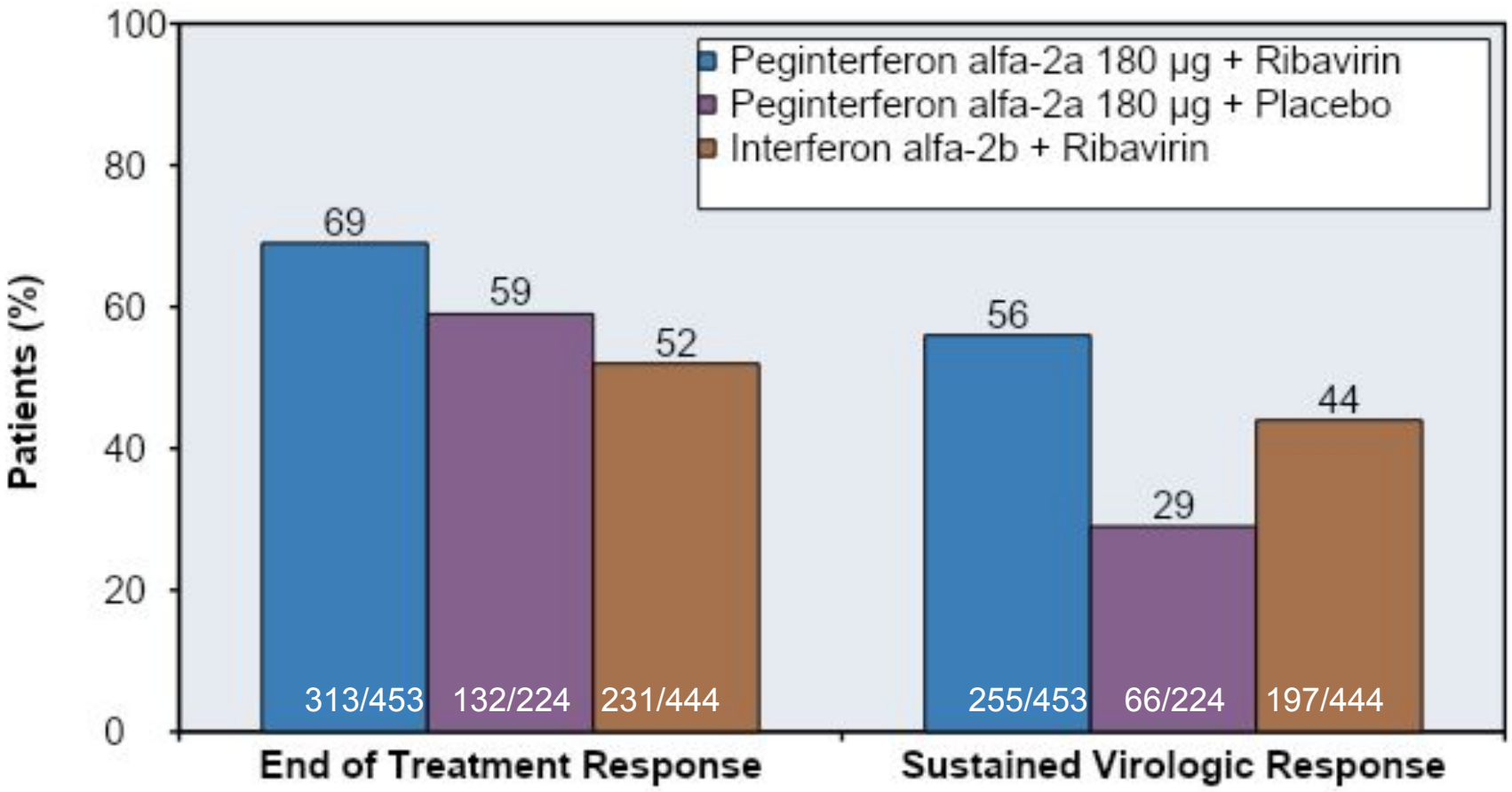
Weight-based Ribavirin (divided bid): 1000 mg/day if < 75kg or 1200 mg/day if ≥ 75kg

Interferon alfa-2b 3 million U 3x/week

Fried MW, et. al. N Engl J Med. 2002;347:975-82.

Peginterferon alfa-2a + Ribavirin for Chronic HCV

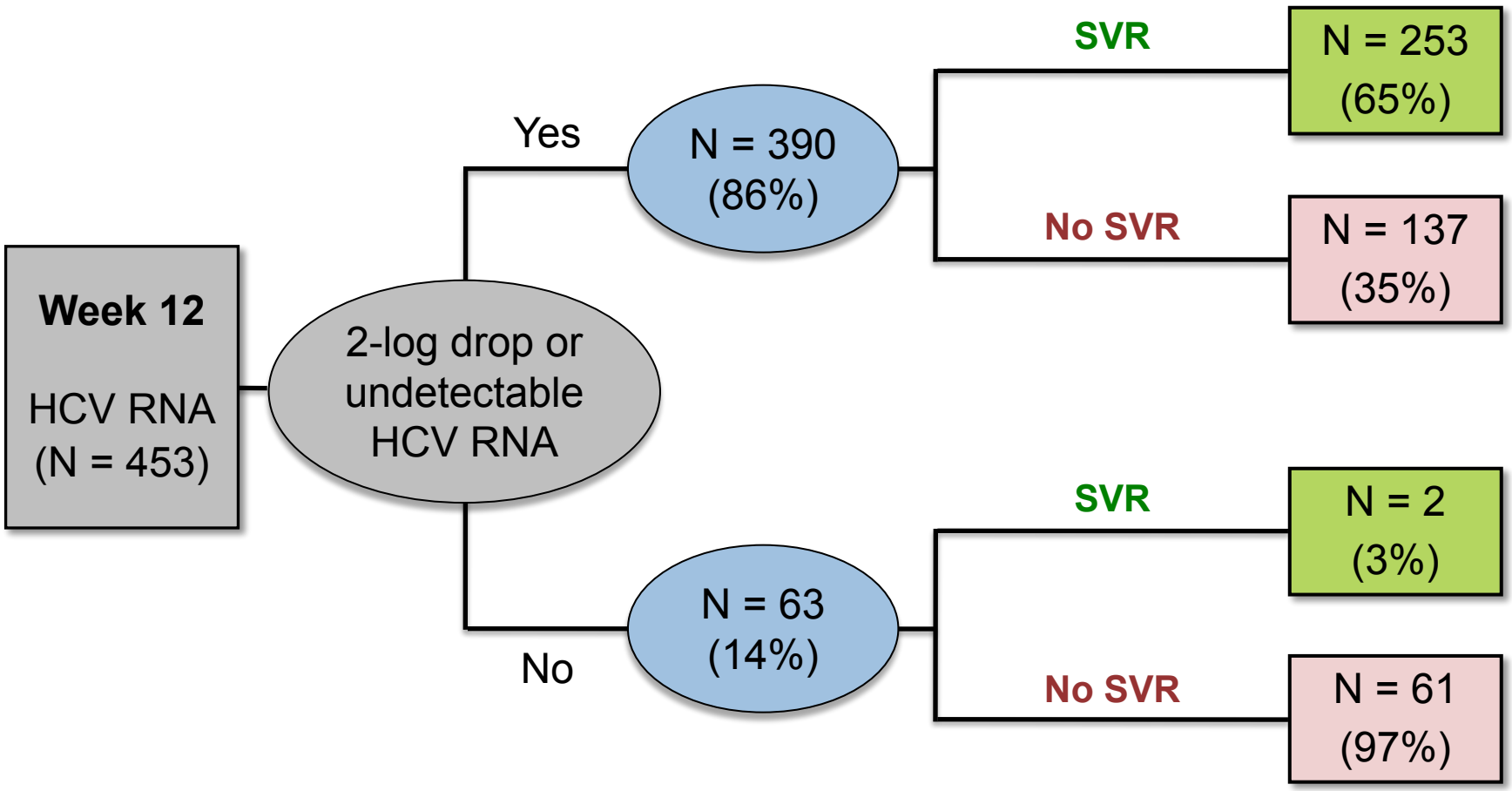
Response after 48 Weeks of Treatment



Fried MW, et. al. N Engl J Med. 2002;347:975-82.

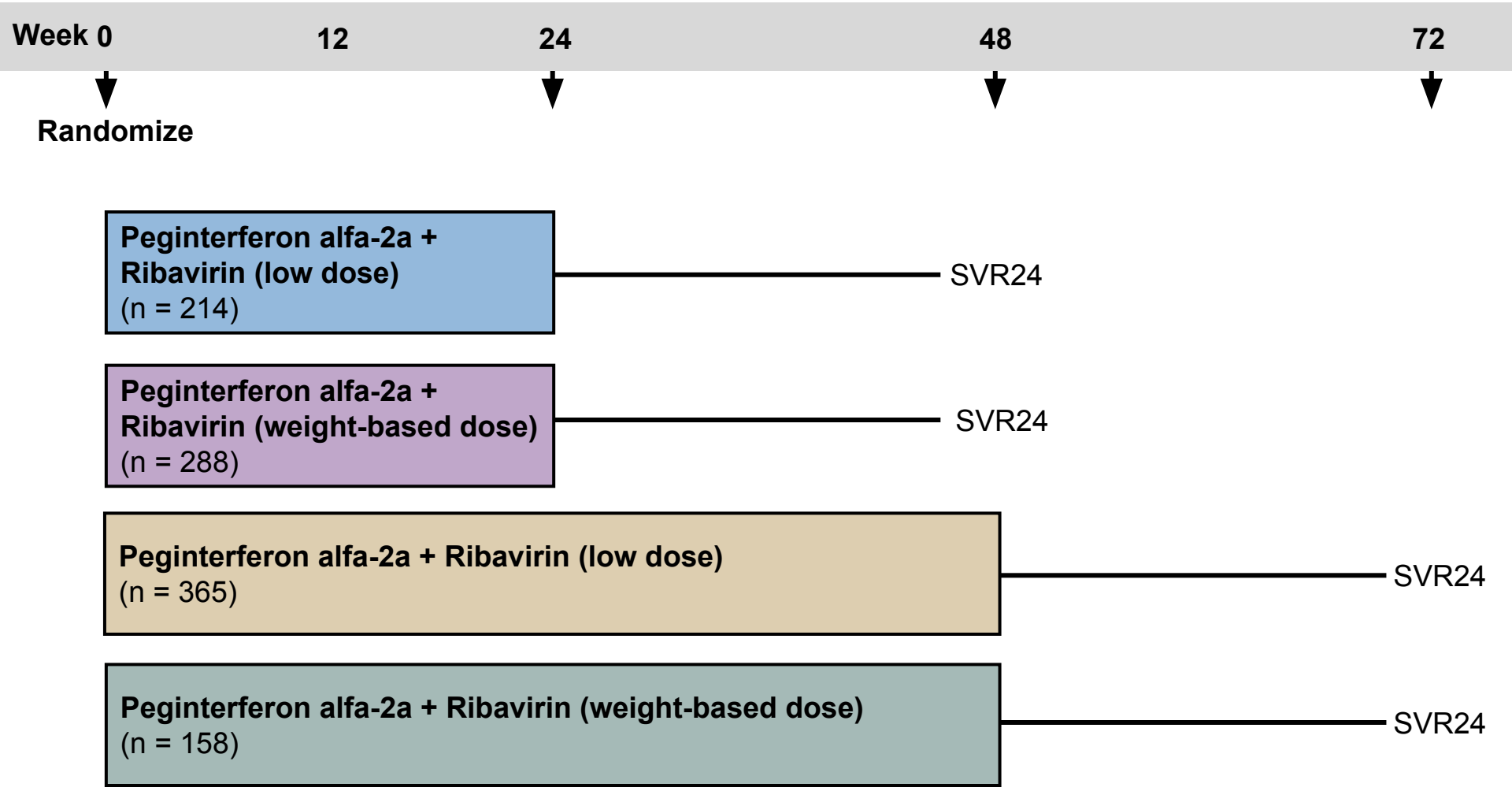
Hepatitis web study

Predictive Value of Early Virologic Response



Fried MW, et. al. N Engl J Med. 2002;347:975-82.

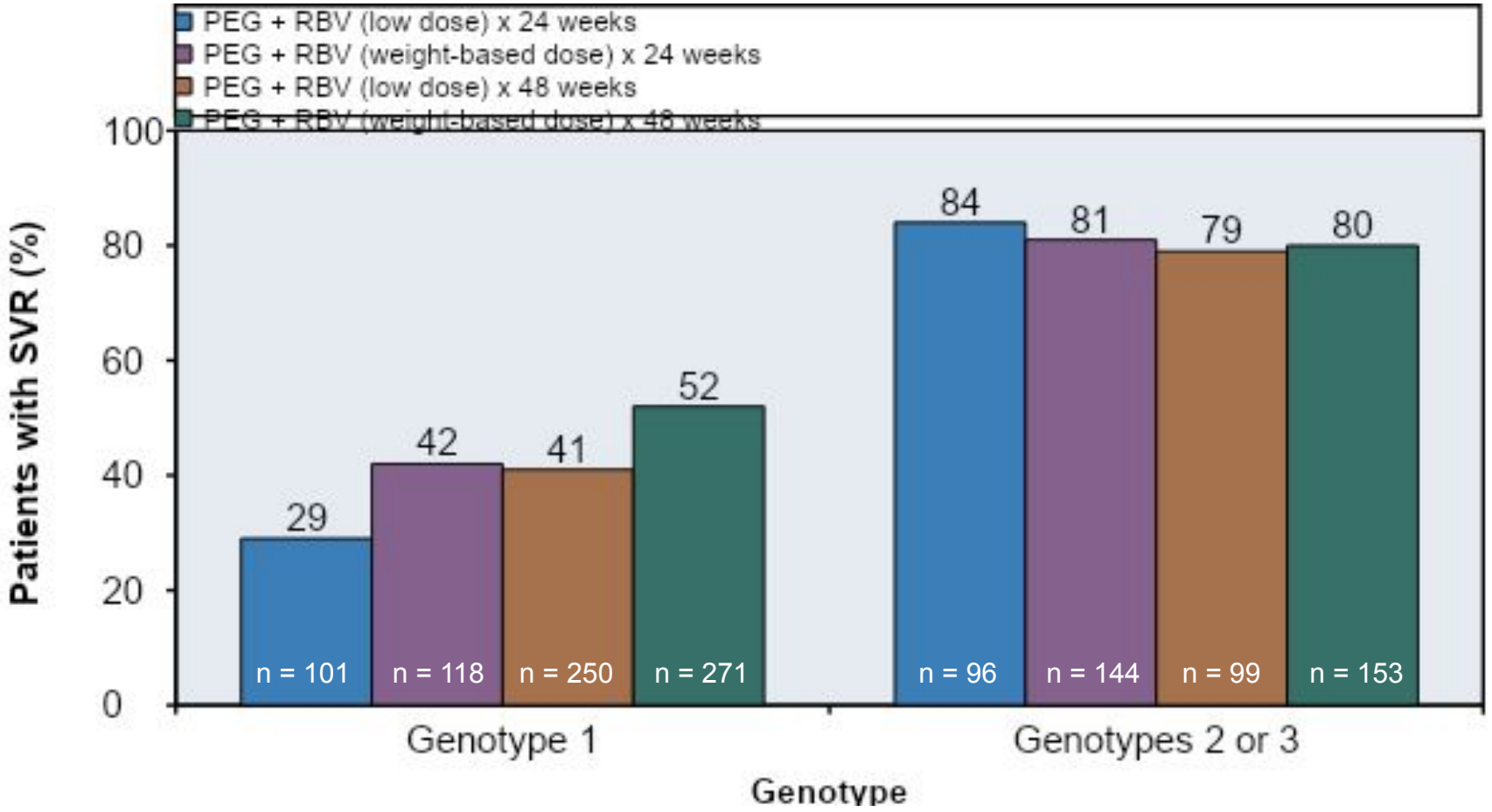
Peginterferon alfa-2a + Ribavirin for Chronic HCV Treatment Duration and Ribavirin Dose



Hadziyannis SJ, et. al. Ann Intern Med. 2004;140:346-55.

Peginterferon alfa-2a + Ribavirin for Chronic HCV Treatment Duration and Ribavirin Dose

SVR24 Rates, by Regimen

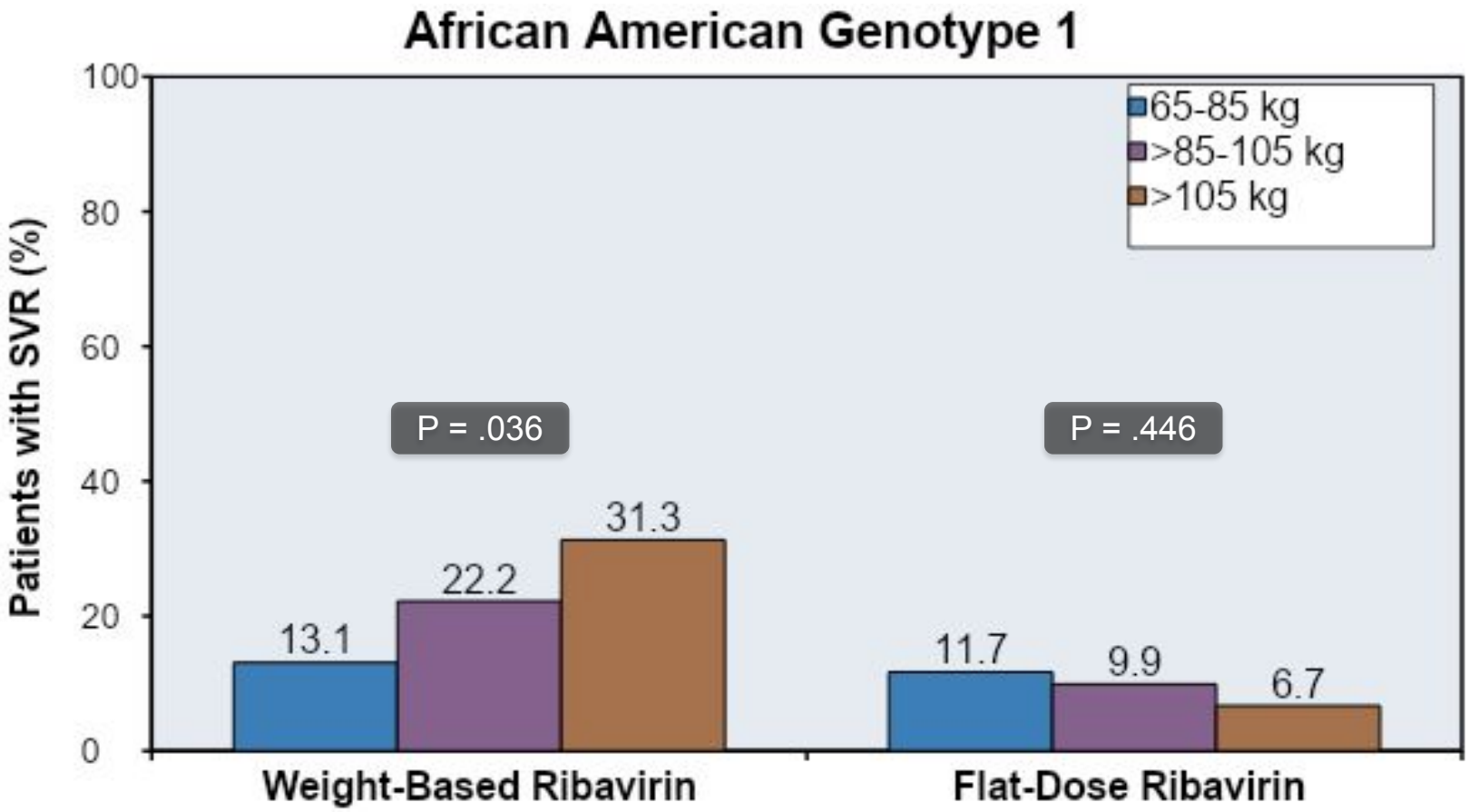


Hadziyannis SJ, et. al. Ann Intern Med. 2004;140:346-55.

Hepatitis web study

WIN-R study: Peginterferon alfa-2b + Ribavirin (weight-based or flat-dose)

Sustained Virologic Response (SVR) by Weight Distribution



Jacobson IM, et. al. Hepatology. 2007;46:971-81.

Hepatitis web study

IDEAL study: Peginterferon alfa-2b + Ribavirin vs Peginterferon alfa-2a + Ribavirin

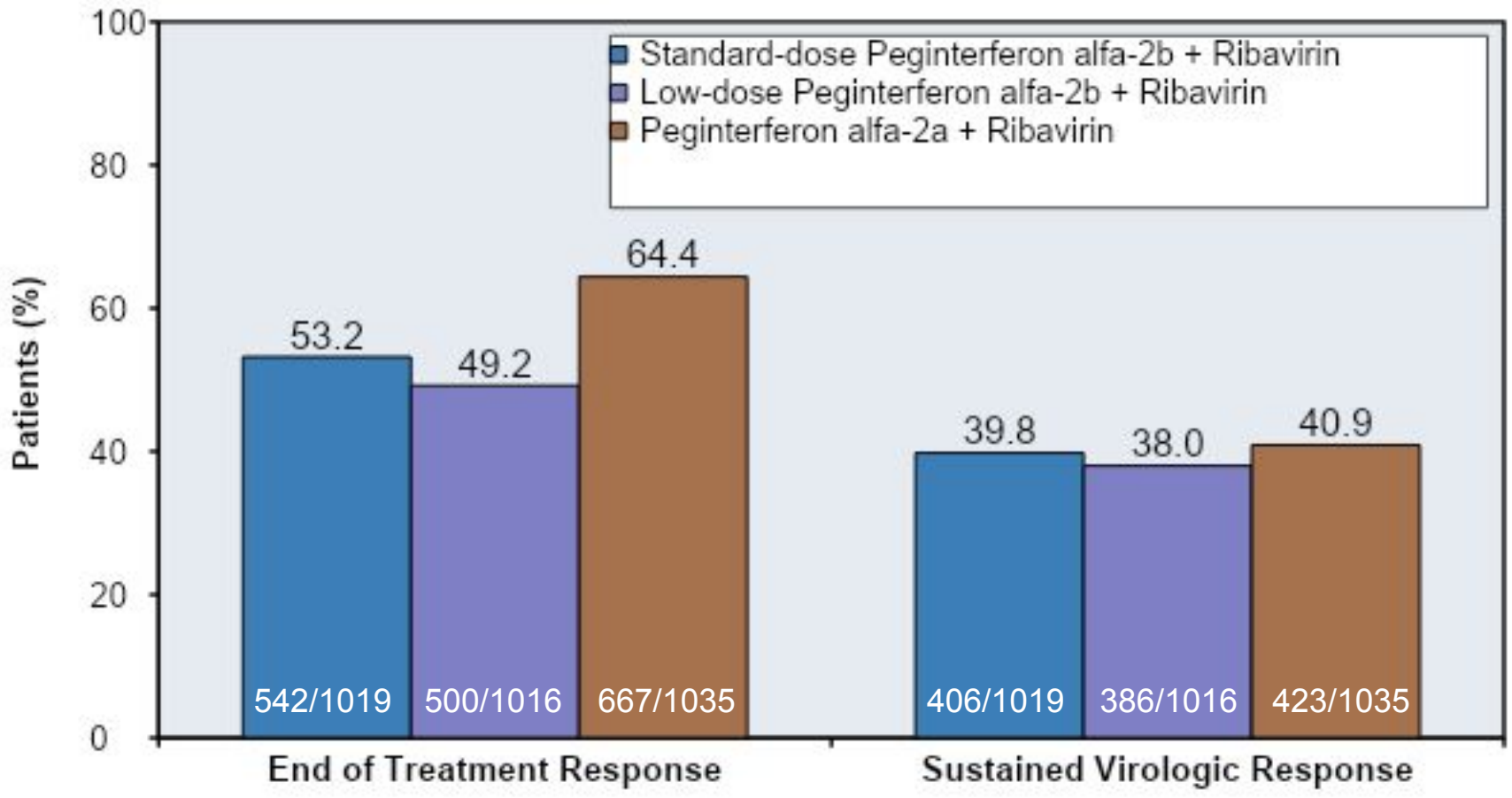
- **Study**
  - Randomized comparative trial
  - 118 centers in United States
- **Subjects**
  - N = 3070 with chronic hepatitis C
  - All genotype 1 (other genotypes excluded)
  - Treatment naïve
  - Subjects were 18 years of age or older
- **Regimens (Ribavirin Dosed by Weight)**
  - Peginterferon alfa-2b: 1.5 µg/kg 1x/week + Ribavirin 800-1400 mg/day*
  - Peginterferon alfa-2b: 1.0 µg/kg 1x/week + Ribavirin 800-1400 mg/day*
  - Peginterferon alfa-2a: 180 µg 1x/week + Ribavirin 1000-1200 mg/day^
- **Primary Endpoint (Sustained Virologic Response [SVR])**
  - SVR = Undetectable Serum HCV RNA 24 weeks after 48-week treatments

*Ribavirin dosing: 40-65 kg: 800 mg/d; >65-85 kg: 1000 mg/d; >85-105 kg: 1200 mg/d; >105-120 kg: 1400 mg/d
^Ribavirin dosing: < 75 kg: 1000 mg/d; ≥ 75 kg: 1200 mg/d

McHutchison JG, et. al. N Engl J Med. 2009;361:580-93.

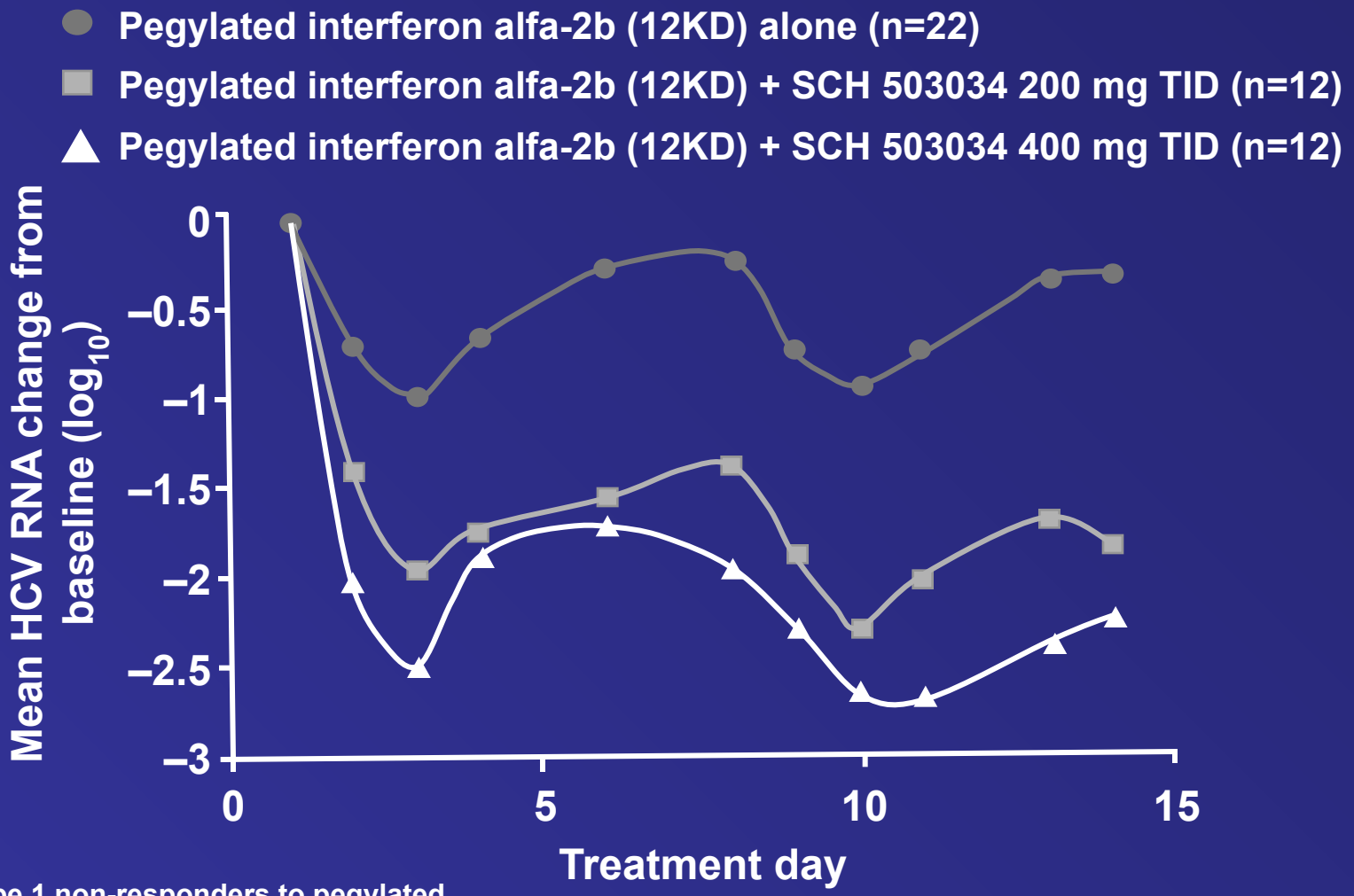
IDEAL results: Peginterferon alfa-2b + Ribavirin vs Peginterferon alfa-2a + Ribavirin

IDEAL Study: Virologic Responses by Treatment Regimen



McHutchison JG, et. al. N Engl J Med. 2009;361:580-93.

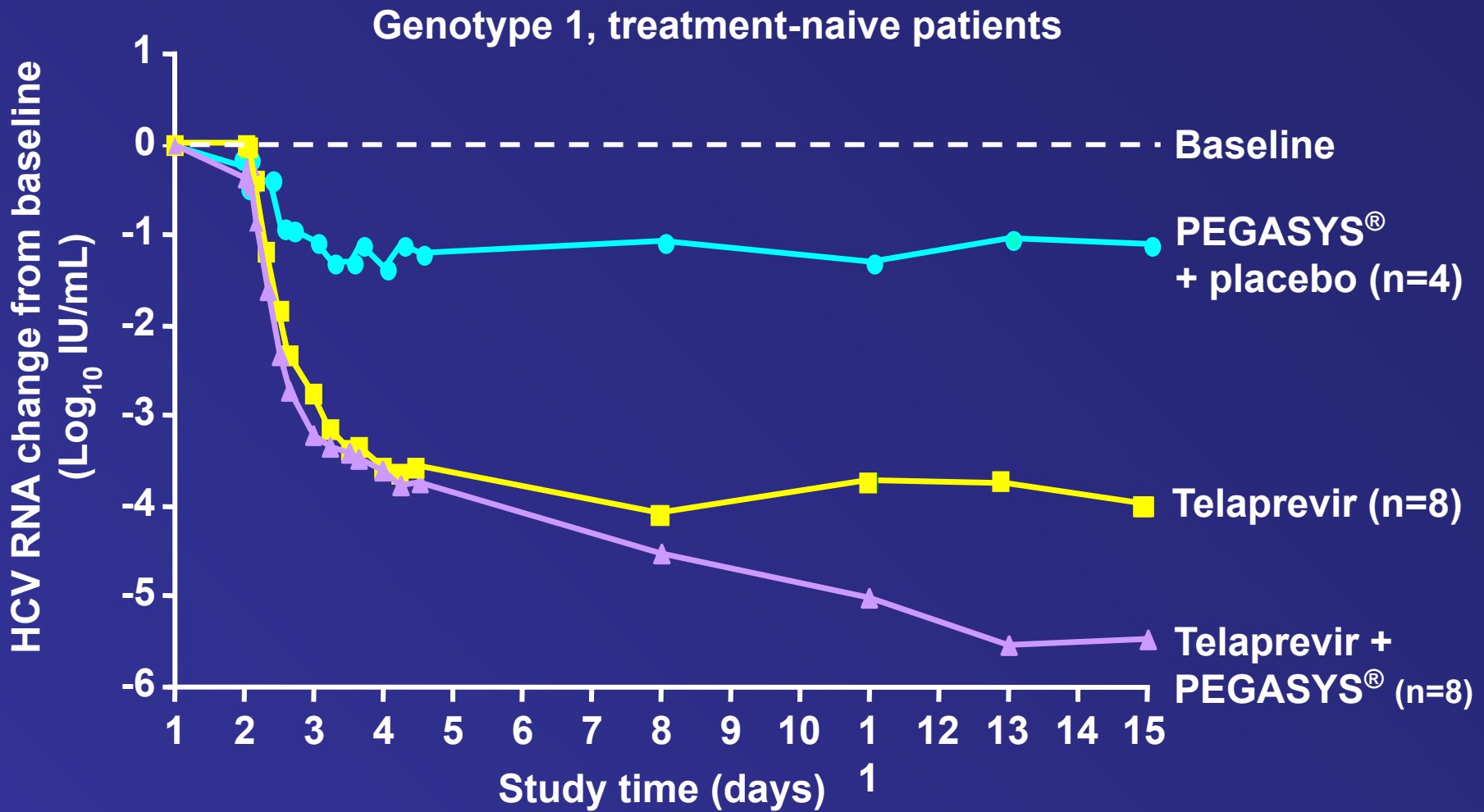
Peg-IFN alfa-2b plus SCH 503034 leads to intraweek viral rebound



Genotype 1 non-responders to pegylated interferon plus ribavirin

Zeuzem S, et al. 56th AASLD 2005; Abstract 201

Synergistic reductions in HCV RNA with telaprevir plus Peg-IFN alfa-2a



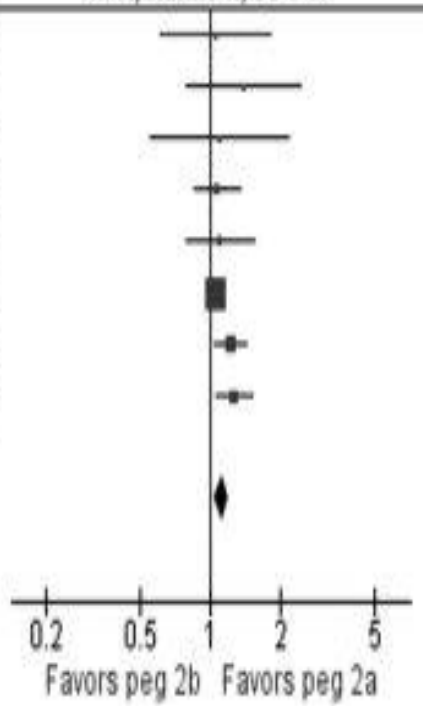
Kieffer TL, et al. Hepatol 2007; 46: 631

Peginterferon alpha-2a vs peginterferon alfa-2b : Systematic review of randomized trials

Study or Subgroup	Peg 2a Events	Peg 2a Total	Peg 2b Events	Peg 2b Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Sinha 2004	14	24	10	18	1.5%	1.05 [0.62, 1.79]	2004
Yenice 2006	18	40	13	40	1.4%	1.38 [0.79, 2.43]	2006
Scotto 2008	14	71	13	72	0.9%	1.09 [0.55, 2.16]	2008
Kolakowska 2008	28	33	27	34	8.6%	1.07 [0.85, 1.34]	2008
Laguno 2009	44	96	36	86	3.9%	1.09 [0.79, 1.52]	2009
McHutchison 2009	423	1035	792	2035	51.8%	1.05 [0.96, 1.15]	2009
Rumi 2009	140	212	119	219	17.9%	1.22 [1.04, 1.42]	2009
Ascione 2009	110	160	87	160	13.9%	1.26 [1.06, 1.51]	2009
Total (95% CI)		**1671**		**2664**	**100.0%**	**1.11 [1.04, 1.19]**	
Total events	791		1097				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 5.65$, $df = 7$ ($P = 0.58$); $I^2 = 0\%$

Test for overall effect: $Z = 3.23$ ($P = 0.001$)



Overall, peginterferon alpha-2a significantly increased the number of patients who achieved an SVR (47%) versus peginterferon alfa-2b (41%) (RR 1.11, 95% CI 1.04–1.19; *P* = 0.004).

Hepatology Volume 51, Issue 4, pages 1176-1184, 23 DEC 2009 DOI: 10.1002/hep.23504

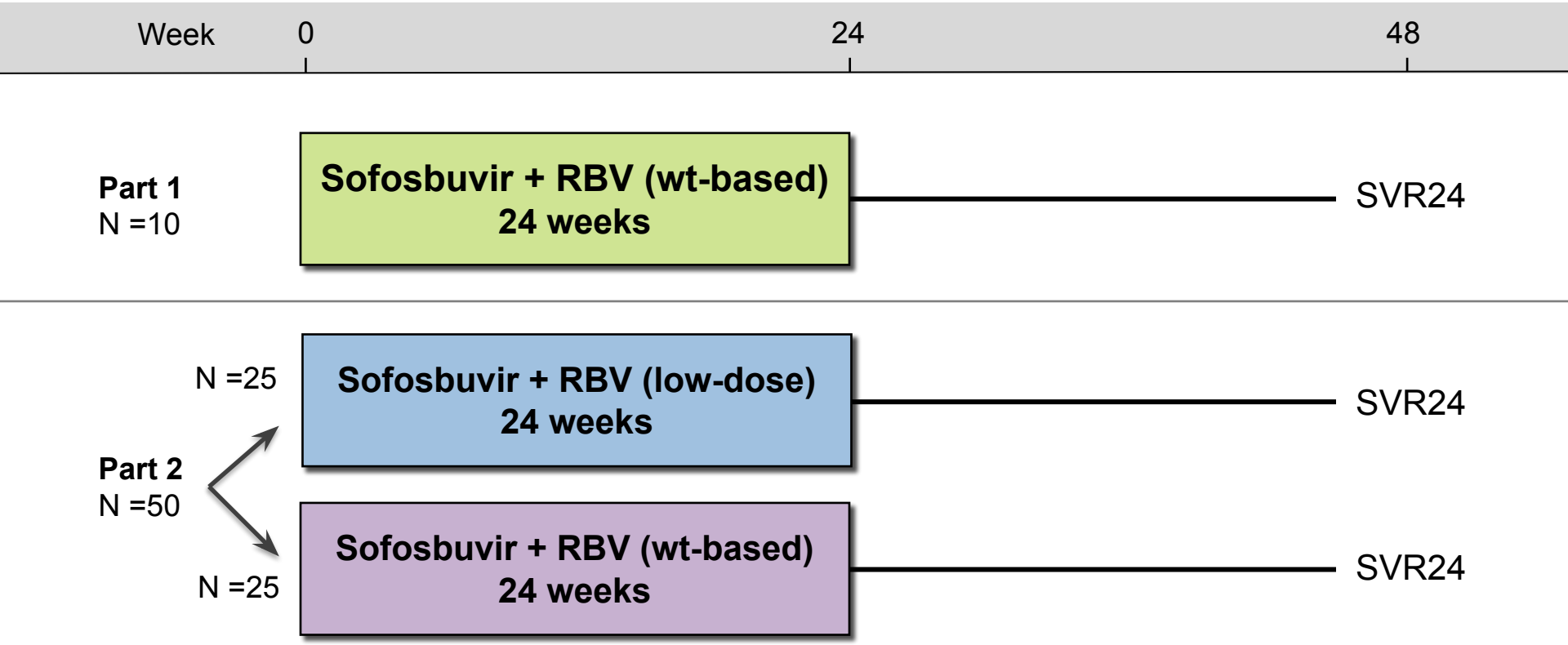
BMI and response to PEG/RBV/PI

- In RESPOND-2, a boceprevir-based trial focusing on previously treated patients, in obese patients (BMI ≥ 30), a 10% lower SVR rate was observed in the RGT group compared with the 48-wk triple treatment group (56% *vs* 65%).
- In the telaprevir-based ADVANCE study, a 12%-16% lower SVR rate was observed in overweight and obese patients compared to normal weight patients.

1.Bacon BR and HCV RESPOND-2 Investigators. Boceprevir for previously treated chronic HCV genotype 1 infection. *N Engl Med* 2011; **364**:1207-1217

2. Jacobson IM and ADVANCE Study Team. Telaprevir for previously untreated chronic hepatitis C virus infection. *N Engl J Med* 2011; **364**: 2405-2416

Sofosbuvir and Ribavirin for Treatment-Naïve HCV GT 1-NIH SPARE Trial



Drug Dosing

Sofosbuvir: 400 mg once daily

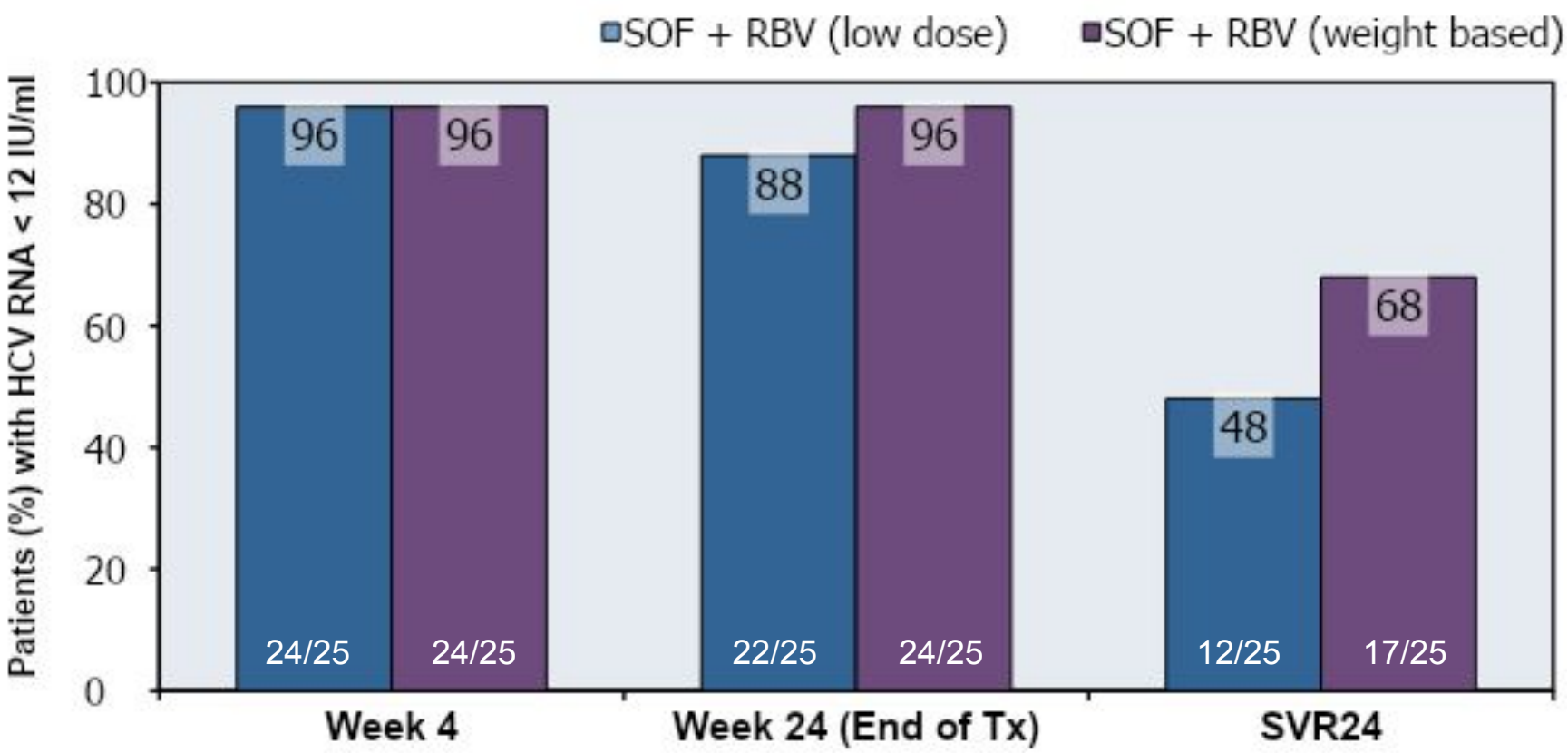
Low-dose Ribavirin (divided bid): 800 mg/day

Weight-based Ribavirin (divided bid): 1000 mg/day if < 75 kg or 1200 mg/day if ≥ 75 kg

Osinusi A, et al. JAMA. 2013;310:804-11.

Sofosbuvir and Ribavirin for Treatment-Naïve HCV GT 1-NIH SPARE Trial: Part 2 Results

NIAID/NIH Part 2: HCV RNA <12 IU/ml by Study Timepoint

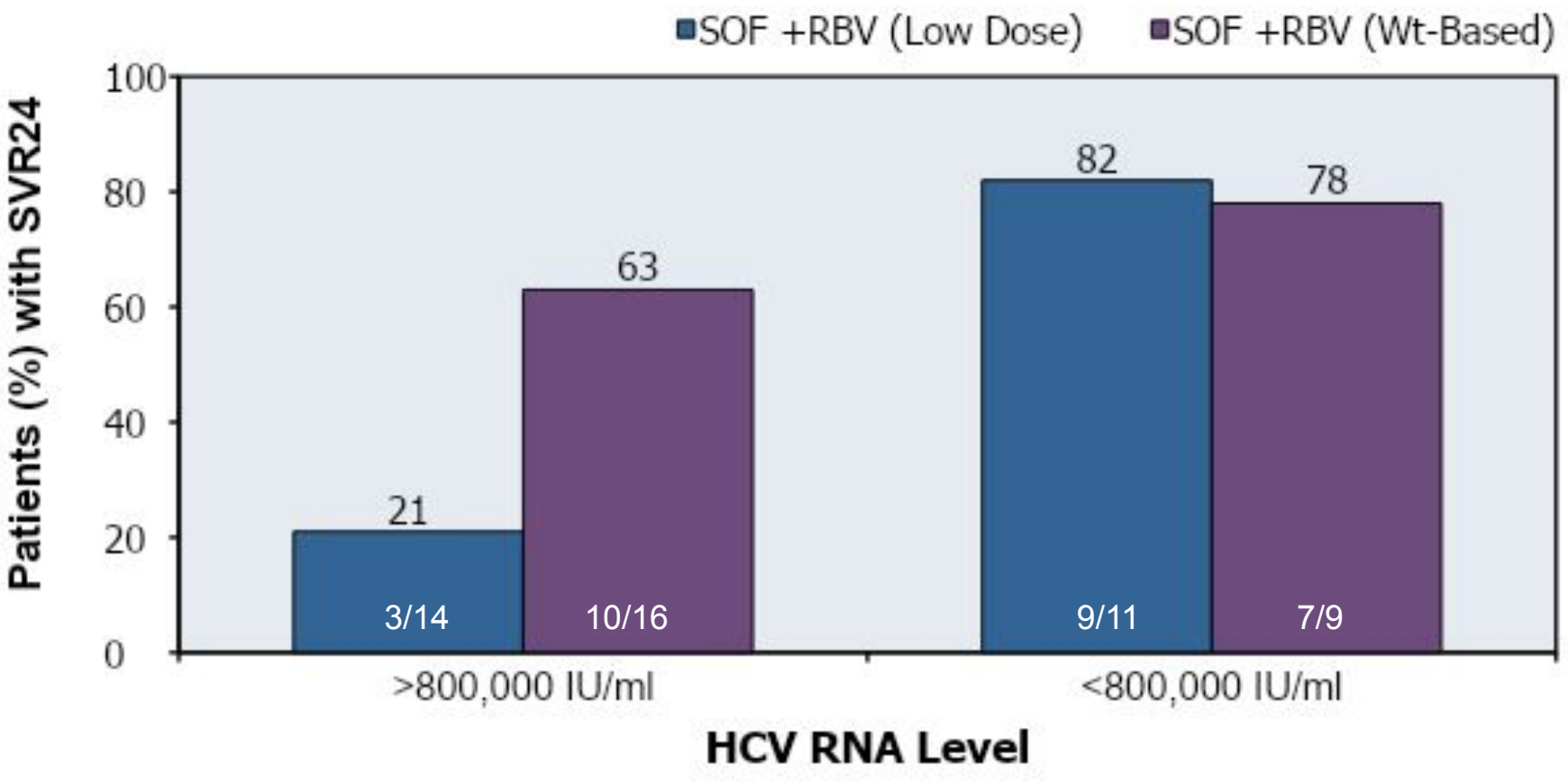


SOF = Sofosbuvir; RBV = Ribavirin

Osinusi A, et al. JAMA. 2013;310:804-11.

Sofosbuvir and Ribavirin for Treatment-Naïve HCV GT 1-NIH SPARE Trial

NIH SPARE Part 2: SVR24 by Baseline HCV RNA Level



SOF= Sofosbuvir; RBV = Ribavirin

Osinusi A, et al. JAMA. 2013;310:804-11.

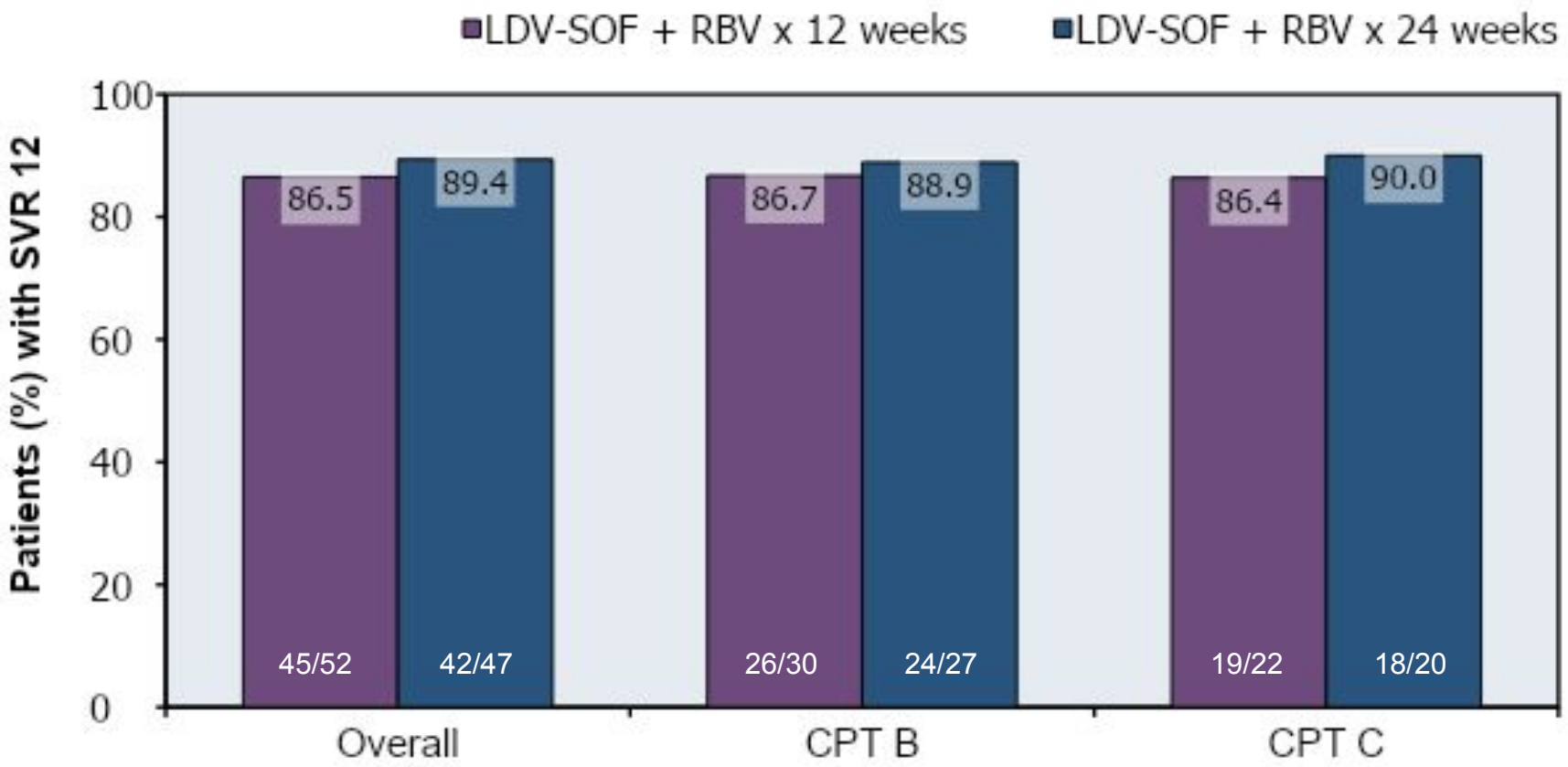
Ledipasvir-Sofosbuvir + Ribavirin in HCV GT 1,4 SOLAR-1 (Decompensated Cirrhosis)

Baseline Characteristic	CTP B		CTP C	
	12-Weeks n=30	24-Weeks n=29	12-Weeks n=23	24-Weeks n=26
Median age, years (range)	60 (28-69)	58 (35-69)	58 (41-71)	59 (48-68)
Male sex, n (%)	22 (73)	18 (62)	14 (61)	18 (69)
White, n (%)	29 (97)	26 (90)	21 (97)	24 (92)
BMI ≥30 kg/m^2, n (%)	10 (33)	10 (34)	13 (57)	9 (35)
HCV RNA, $\log_{10}$ IU/ml (median)	5.9	5.8	5.6	5.8
IL28B non CC, n (%)	26 (87)	23/28 (82)	17 (74)	19 (73)
HCV Genotype 1a, n (%) 4, n (%)	 19 (63) 1 (3)	 22 (76) 0	 15 (65) 2 (9)	 18 (69) 0
Prior Treatment	22 (73)	19 (65)	11 (48)	18 (69)

Flamm SL, al. 65th AASLD. 2014: Abstract 239.

Hepatitis web study

Ledipasvir-Sofosbuvir + Ribavirin in HCV GT 1,4 SOLAR-1 (Decompensated Cirrhosis)



6 subjects excluded because received transplant while on study: (2 CPT B/24 week; 1 CPT 2/12 week; 3 CPT C/24 week
3 subjects had not reached SVR12 timepoint

Flamm SL, al. 65th AASLD. 2014: Abstract 239.

Hepatitis web study

Obesity epidemic in HIV patients

Studies show that 6 out of 10 HIV+ people are overweight/obese

"More than 70% of the patients were on HAART at the time of the study.
Neither duration of HAART nor the type of regimen influenced BMI values. " (Amorosa, 2005)

Crum et al. (2008) Obesity among patients with HIV: The latest epidemic. *AIDS patient care and STDs* .
Amorosa V et al. (2005) *A tale of two epidemics. The intersection between obesity and HIV infection in Philadelphia*. J Acquir Immune Defic Syndr

Obesity and survival in HIV

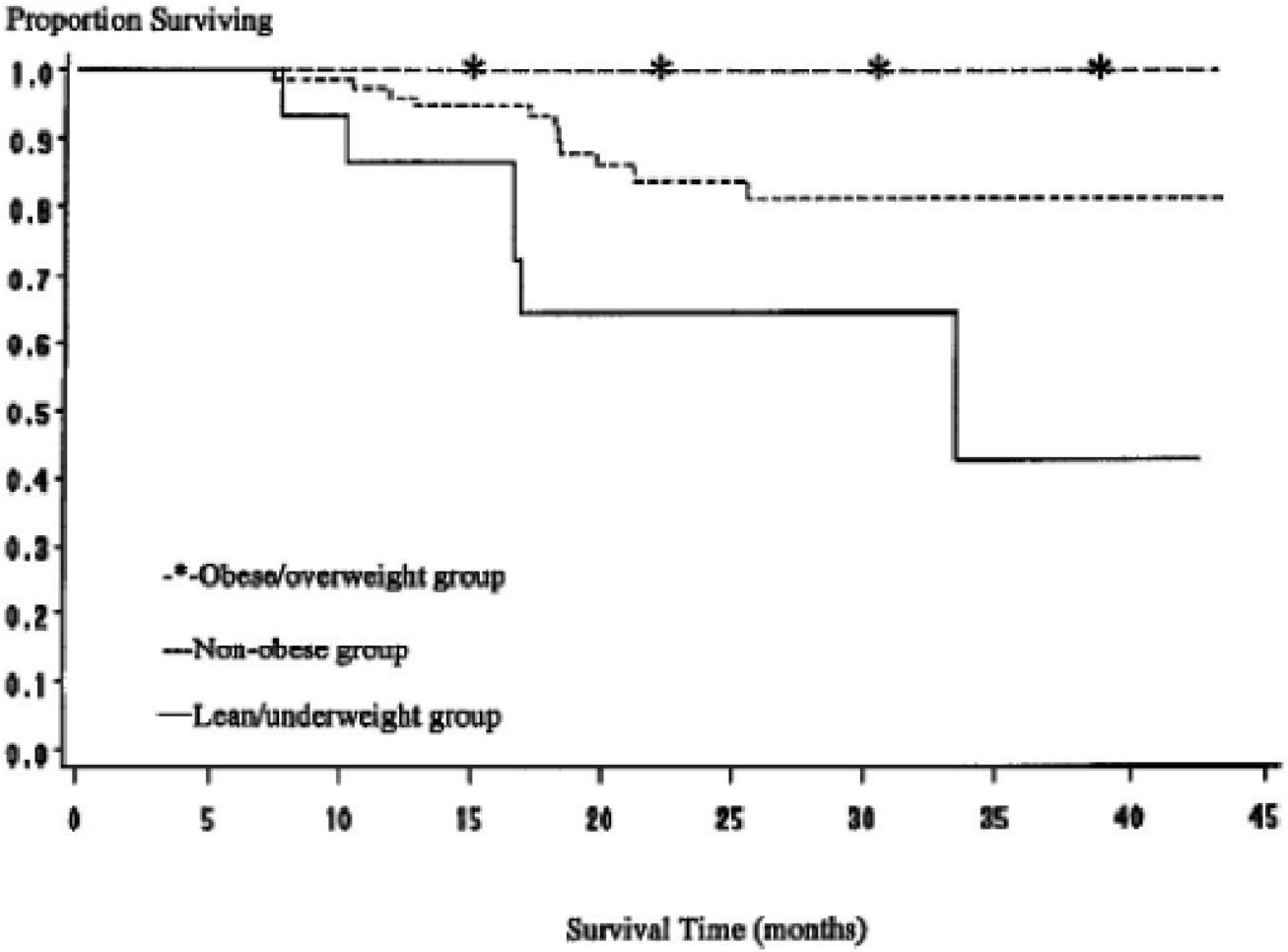


FIG. 1. Kaplan-Meier plot depicting decreased survival time in both the lean and nonobese HIV-1–seropositive drug users.

Efavirenz and obesity project

- While effective ART has reduced the prevalence of HIV-associated wasting, the prevalence of obesity has increased[1]
- Obesity is characterized by physiological changes which can impact on drug pharmacokinetics[2] as well as immune responses[3]
- Treatment failure has been reported in an obese patient receiving a standard efavirenz (EFV) dose[4]
- Physiologically-based pharmacokinetic modelling shows that EFV dose increase is needed to maintain sufficient levels in obese individuals[4]
- Obesity may therefore be a risk factor for EFV underdosing and, thus, for virological failure

[1]Crum-Cianflone N et al. AIDS 2010; [2]Brill M et al. Clin Pharmacokinet 2012; [3]Koethe JR et al. JID 2013; [4]de Roche M et al. AVT 2012

Aim of the project

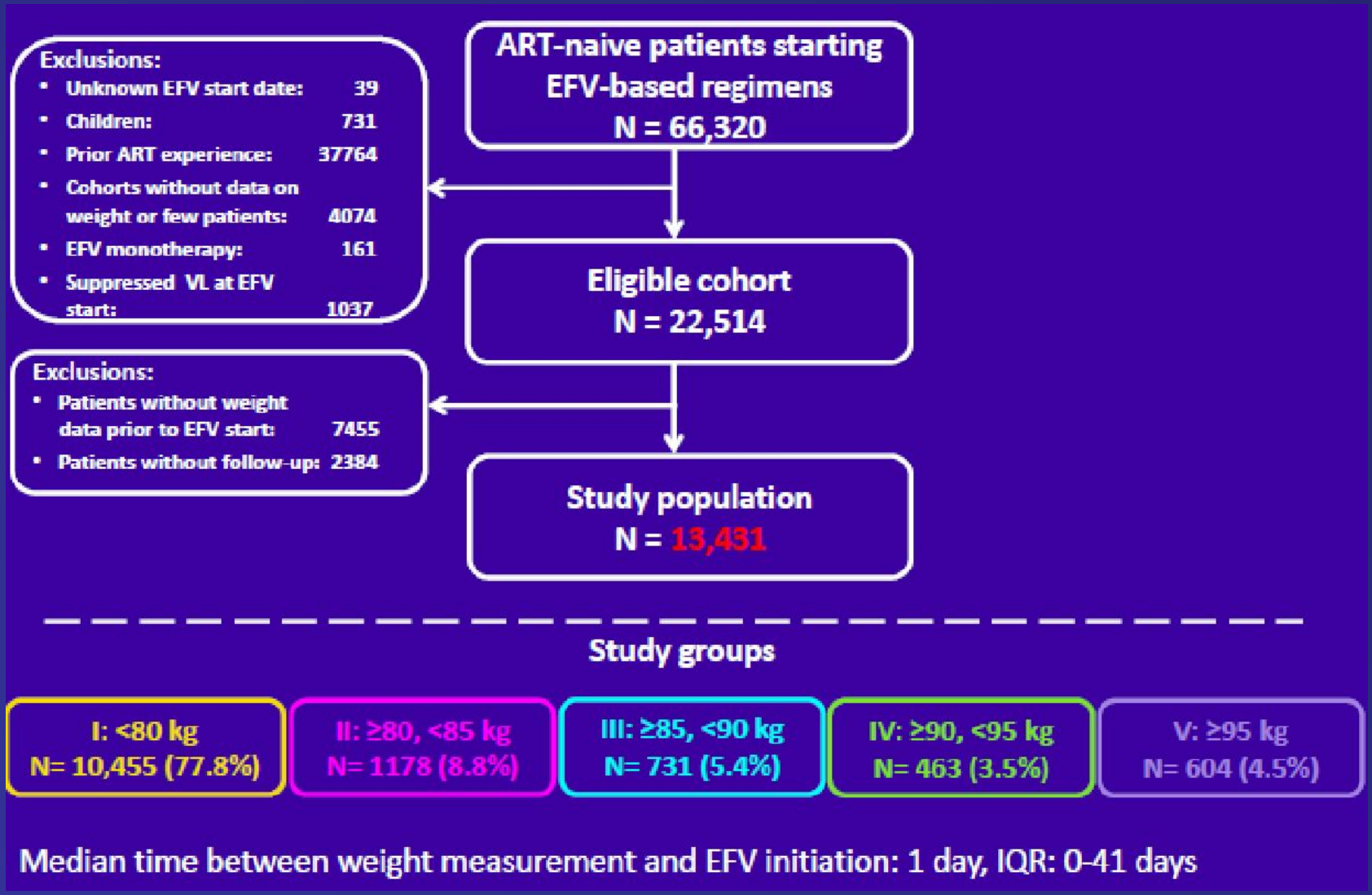
- To use data from COHERE[1], a collaboration of 33 cohorts across Europe, to compare:
  - the time to initial viral suppression after treatment initiation, and
  - the time to virological rebound after initial suppression

  in obese and non-obese ART-naive patients starting an EFV-based regimen

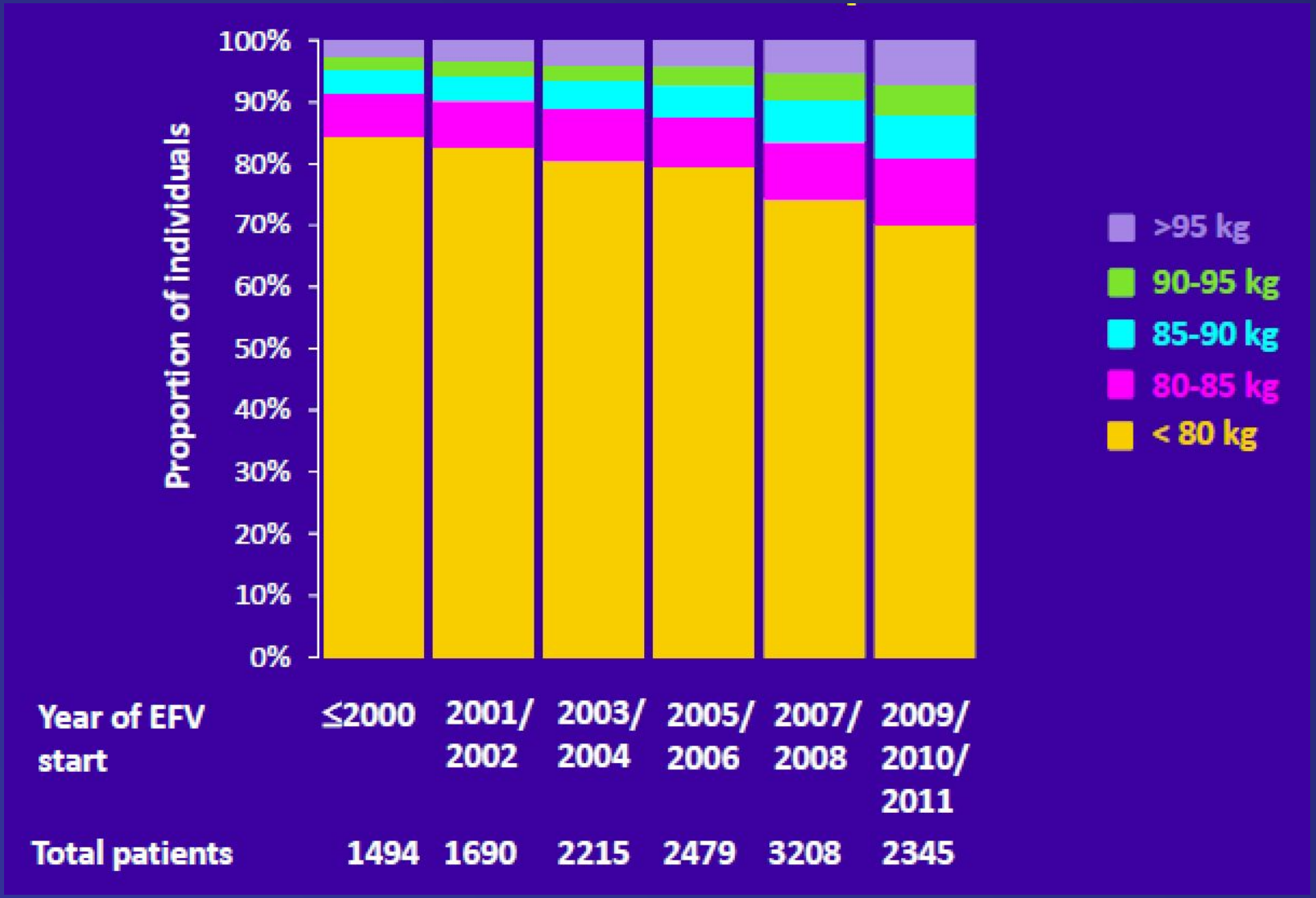
- Patients were grouped according to weight:
  - Group I: <80 kg
  - Group II: ≥80, <85 kg
  - Group III: ≥85, <90 kg
  - Group IV: ≥90, <95 kg
  - Group V: ≥95 kg

[1]COHERE: Collaboration of Observational HIV Epidemiological Research Europe

Selection of the study population



Weight distribution of patients starting EFV



Median time to undetectability

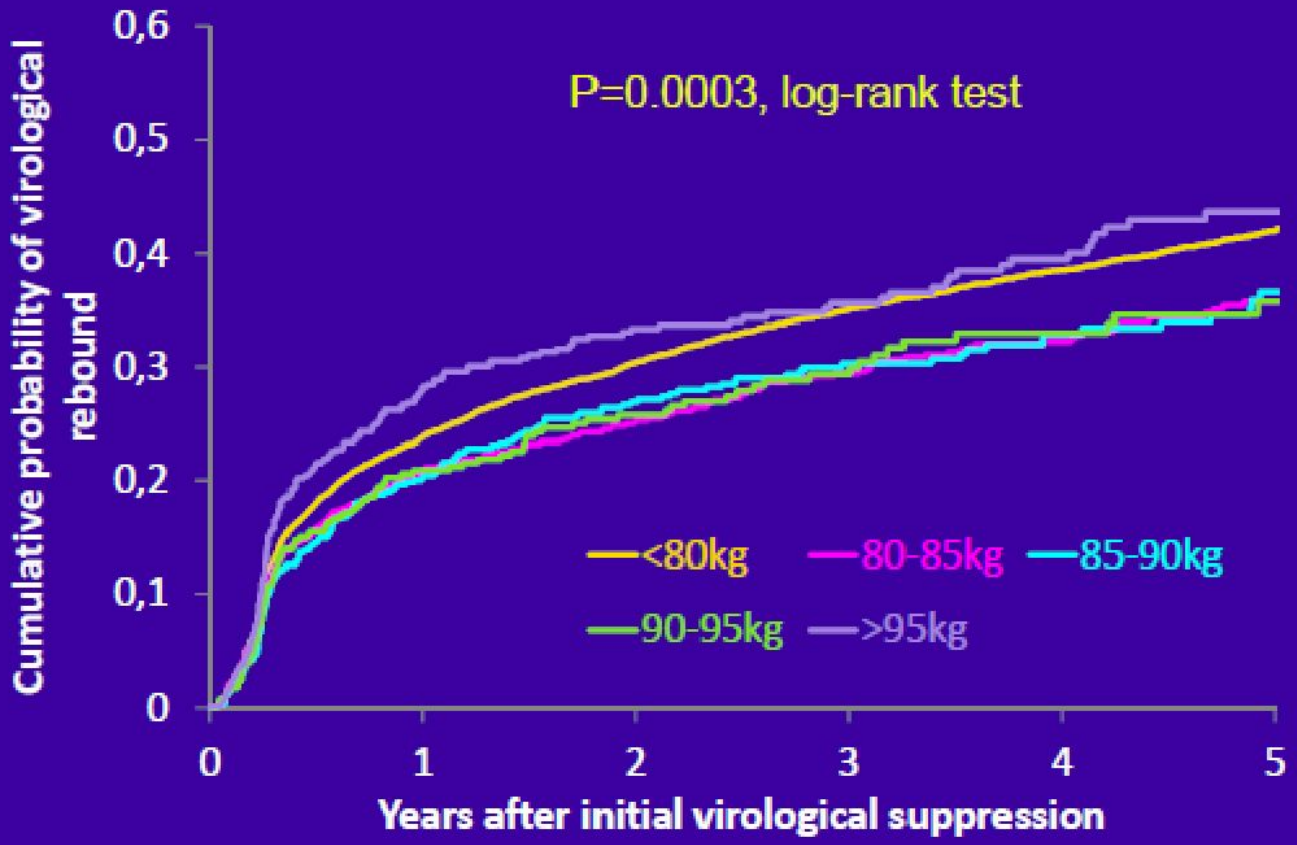
- Overall, 11310 (84.2%) experienced an undetectable VL after EFV start
- Median time to initial undetectable VL (Kaplan-Meier analysis)

Weight <80kg:	0.39 years
Weight ≥80, <85kg:	0.36 years
Weight ≥85, <90kg:	0.38 years
Weight ≥90, <95kg:	0.38 years
Weight ≥95kg:	0.35 years

P = 0.0001, log-rank test

Time to virological rebound

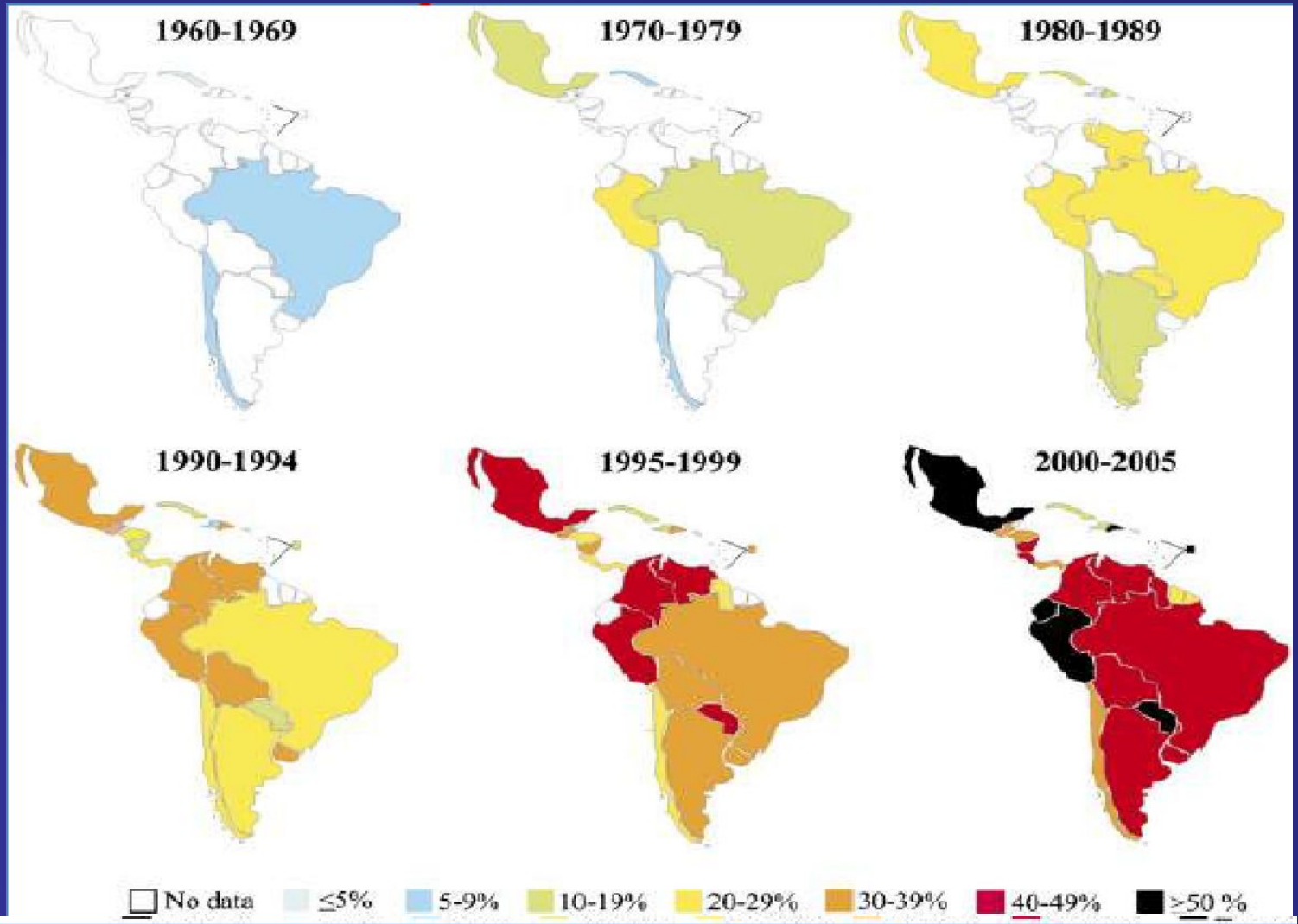
- Of the 11310 patients with an undetectable VL, 3867 (34.2%) subsequently experienced viral load rebound



Conclusions

- No significant differences seen between groups in time to initial undetectable VL, however time tended to be shorter for those with weight ≥95 kg vs. <80 kg
- Probability of VL rebound was significantly higher for those with weight ≥95 kg vs. <80 kg
- Association with time to VL rebound was predominantly seen in white individuals and in men, suggesting the presence of gender and ethnicity-related differences in drug exposure and/or obesity-induced immunomodulatory activity
- Response to EFV should be monitored carefully in patients with severe obesity; TDM might be a useful tool

Epidemic of obesity in South America and Caribbean



Rueda-Clausen[4], Silva[4] and López-Jaramillo (March 2008) Epidemic of overweight and obesity in Latin America and the Caribbean, International Journal of Cardiology.

Factors Associated With Death or Hospitalization Due to Pandemic 2009 Influenza A(H1N1) Infection in California

JAMA. 2009;302(17):1896-1902. doi:10.1001/jama.2009.1583

Table 2. Comorbid Conditions of Reported Hospitalized and Fatal Cases of Pandemic 2009 Influenza A(H1N1) Infections in California, April 23 Through August 11, 2009

		Cases Aged 0-17 Years		Cases Aged ≥18 Years	
	All Cases (N = 1088)	Fatal (n = 8)	Nonfatal (n = 336)	Fatal (n = 110)	Nonfatal (n = 634)
Chronic comorbid illness associated with severe influenza[a]	741 (68)	6 (75)	199 (59)	83 (75)	453 (71)
Chronic lung disease	403 (37)	3 (38)	126 (38)	45 (41)	229 (36)
Asthma	257 (24)	1 (13)	99 (29)	18 (16)	139 (22)
Other/unknown[b]	146 (13)	2 (25)	27 (8)	27 (25)	90 (14)
Chronic cardiac disease[c]	167 (15)	2 (25)	25 (7)	25 (23)	115 (18)
Metabolic disease	223 (20)	2 (25)	23 (7)	38 (35)	160 (25)
Diabetes mellitus	116 (11)	0	4 (1)	20 (18)	92 (14)
Renal disease	72 (7)	0	8 (2)	18 (16)	46 (7)
Other/unknown[d]	59 (5)	2 (25)	11 (3)	7 (6)	39 (6)
Immunosuppressive conditions	205 (19)	3 (38)	55 (16)	36 (33)	111 (18)
Cancer/transplant/immunosuppressive drugs[e]	155 (14)	2 (25)	42 (13)	29 (26)	82 (13)
HIV/AIDS	22 (2)	0	0	4 (4)	18 (3)
Other/unknown	31 (3)	1 (13)	13 (4)	4 (4)	13 (2)
Neuromuscular disorder[f]	115 (11)	4 (50)	45 (13)	14 (13)	52 (8)
Pregnancy[g]	97/1012 (10)	0	5 (2)	6/104 (6)	86/587 (15)
Other chronic comorbid illness[a]	370 (34)	2 (25)	45 (13)	69 (63)	254 (40)
Obesity[g,h]	172/361 (48)	0	15 (19)	46/68 (66)	111/212 (52)
BMI 30-34.9	55 (35)			11 (24)	44 (40)
BMI 35-39.9	34 (22)			12 (26)	22 (20)
BMI ≥40	67 (43)			23 (50)	44 (40)
Gastrointestinal tract	109 (10)	2 (25)	29 (9)	12 (11)	66 (10)
GERD	34 (3)	1 (13)	5 (2)	4 (4)	24 (4)
Other/unknown[i]	75 (7)	1 (13)	24 (7)	8 (7)	42 (7)
Hyperlipidemia	33 (3)	0	0	2 (2)	31 (5)
Hypertension	176 (16)	0	2 (<1)	27 (25)	147 (23)

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; GERD, gastroesophageal reflux disease; HIV, human immunodeficiency virus.

[a] Conditions listed are not mutually exclusive because of the presence in some patients of multiple underlying chronic diseases.

[b] Includes chronic obstructive pulmonary disease, bronchopulmonary dysplasia/respiratory distress syndrome, bronchiolitis obliterans organizing pneumonia, Sjögren syndrome, and obstructive sleep apnea.

[c] Includes congenital heart disease, atrial fibrillation, status post–aortic valve replacement, congestive heart failure, hypertensive heart disease, and coronary artery disease.

[d] Includes pituitary, thyroid, and adrenal disorders.

[e] Includes immunosuppressive drugs, cancer, congenital immunodeficiency, leukemia, and organ transplantation.

[f] Includes cerebral palsy, seizure disorder, developmental delay, Parkinson disease, muscular dystrophy, quadriplegia, and mental retardation.

[g] Includes only cases with known information.

[h] Includes cases aged 2 to 19 years where BMI for age was at least 95th percentile and cases aged at least 20 years where BMI was at least 30; excludes pregnant cases (103 cases were <2 years).

[i] Includes status post–gastrostomy tube placement, gastritis, cholelithiasis, history of small bowel obstruction, short gut syndrome, pyloric stenosis, and Hirschsprung disease.

Use of Intravenous Neuraminidase Inhibitors During the 2009 Pandemic: Results From Population-Based Surveillance

JAMA. 2011;306(2):160-162. doi:10.1001/jama.2011.950

Table. Characteristics of Patients Hospitalized With Laboratory-Confirmed pH1N1 Infection Who Received US FDA Licensed and Experimental IV Neuraminidase Inhibitors: Emerging Infections Program Influenza-Associated Hospitalization Surveillance, April 2009-April 2010[a]

	No. (%)					
	Total		Children		Adults	
	Licensed NAI (n = 6175)[b]	IV NAI (n = 41)	Licensed NAI (n = 1941)[b]	IV NAI (n = 3)	Licensed NAI (n = 4234)[b]	IV NAI (n = 38)
Age, median (range), y	32 (0-101)	40 (3-67)	4 (0-17)	4 (3-14)	47 (18-101)	41 (19-67)
Any underlying medical condition[c]	4804 (78)	36 (88)[d]	1096 (56)	2 (67)[d]	3708 (88)	34 (89)[d]
Asthma	1936 (31)	8 (20)[d]	660 (34)	1 (33)[d]	1276 (30)	7 (18)[d]
Other chronic lung diseases	827 (13)	4 (10)[d]	89 (5)	0	738 (17)	4 (11)[d]
Diabetes mellitus	970 (16)	5 (12)[d]	21 (1)	0	949 (22)	5 (13)[d]
Morbid obesity	471 (8)	7 (17)[d]	NA	NA	471 (11)	7 (18)[d]
Obesity	1077 (17)	18 (44)[d]	193 (10)	1 (33)[d]	884 (21)	17 (45)[d]
Immunosuppressive condition	654 (11)	3 (7)[d]	95 (5)	0	559 (13)	3 (8)[d]
Cardiovascular disease	895 (14)	5 (12)[d]	86 (4)	0	809 (19)	5 (13)[d]
Chronic renal disease	458 (7)	0	34 (2)	0	424 (10)	0
Pregnant	417 (7)	3 (7)[d]	28 (1)	0	389 (9)	3 (8)[d]
Diagnosed with ARDS	231 (4)	24 (59)[d]	41 (2)	0	190 (4)	24 (63)[d]
Diagnosed with pneumonia	2373 (38)	29 (71)[d]	656 (34)	2 (67)[d]	1717 (41)	27 (71)[d]
Mechanical ventilation	649 (11)	37 (90)[d]	116 (6)	2 (67)[d]	533 (13)	35 (92)[d]
Extracorporeal membrane oxygenation	28 (0)	4 (10)[d]	7 (0)	2 (67)	21 (0)	2 (5)[d]
Intensive care unit admission	1379 (22)	38 (93)[d]	379 (20)	2 (67)[d]	1000 (24)	36 (95)[d]
Hospitalization, median (range), d	3 (0-199)	23 (6-117)[d]	2 (0-102)	9 (8-25)[d]	3 (0-199)	23 (6-117)[d]
Died	174 (3)	11 (27)[d]	16 (1)	2 (67)[d]	158 (4)	9 (24)[d]
Onset of symptoms until any NAI begun, median (range), d	3 (0-71)	6 (1-11)[d]	2 (0-50)	6 (2-10)	3 (0-71)	6 (1-11)[d]
Received oseltamivir during hospitalization	6151 (100)	41 (100)	1937 (100)	3 (100)	4214 (100)	38 (100)
Received oseltamivir before IV NAI	NA	36 (88)	NA	3 (100)	NA	33 (87)
Time receiving oseltamivir before IV NAI, median (range), d	NA	3 (0-12)	NA	3 (2-5)	NA	3 (0-12)
Simultaneous use of both oseltamivir and IV NAI for ≥2 d	NA	10 (24)	NA	2 (67)	NA	8 (21)
Both oseltamivir and IV NAI, median (range), d	NA	5 (3-12) (n = 10)	NA	3 (3) (n = 2)	NA	6 (4-12) (n = 8)
Duration of IV NAI, median (range), d	NA	9 (1-20)	NA	3 (3-6)	NA	9 (1-20)

Abbreviations: ARDS, acute respiratory distress syndrome; FDA, Food and Drug Administration; IV, intravenous; NA, not applicable; NAI, neuraminidase inhibitor; pH1N1, 2009 pandemic influenza A(H1N1) virus.

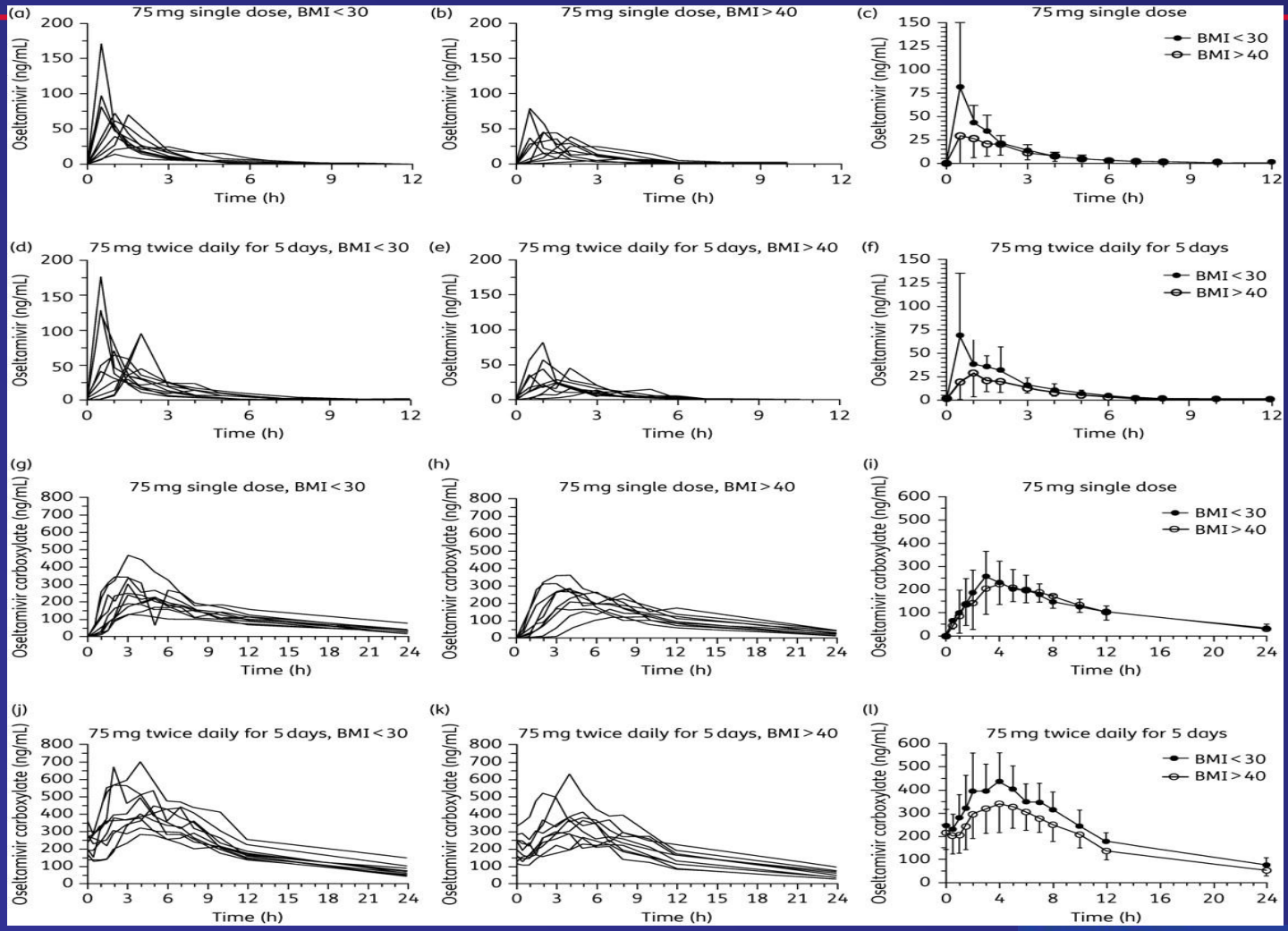
[a] US FDA–licensed NAIs included oral oseltamivir and inhaled zanamivir. Experimental NAIs included IV peramivir and IV zanamivir. Reported doses of IV zanamivir and peramivir were 400 mg and 600 mg twice a day, respectively (or equivalent dose for children and patients with renal failure). The emergency use authorization for peramivir was issued on October 23, 2009. Prior to this date, peramivir was available by emergency investigational new drug (eIND). Zanamivir was available by eIND. Emergency use authorization indications for peramivir included no response to oseltamivir or zanamivir, need for IV drug delivery, and clinical judgment by the health care provider[e]; no criteria existed for eIND.

[b] Patients received only licensed NAIs.

[c] Medical conditions include asthma; chronic lung, cardiovascular, and metabolic disease; renal disease; cancer diagnosis in previous 12 months; hemoglobinopathy; neuromuscular disorders; immunosuppressive condition; seizure disorder; history of leukemia or lymphoma; cognitive dysfunction; cystic fibrosis; obesity; morbid obesity; abnormality of upper airway (children only); and pregnancy.

[d] $P \leq .05$ by χ^2 test (categorical variables) or Wilcoxon rank sum test (continuous variables) comparing patients who received only licensed NAIs with those who ever received an IV NAI.

Oseltamivir and oseltamivir carboxylate plasma concentrations in control (BMI<30) and morbidly obese (BMI>40) subjects.



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Journal of Antimicrobial Chemotherapy