Mini Conferência
Tratamento da hepatite C em pacientes Co-infectados pelo HIV/virus C
Dos ensaios clínicos aos guidelines

II Forum Hepatite C/HIV

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Conflito de Interesse

- Recebo remuneração por palestras e/ou consultorias das seguintes industrias farmacêuticas:

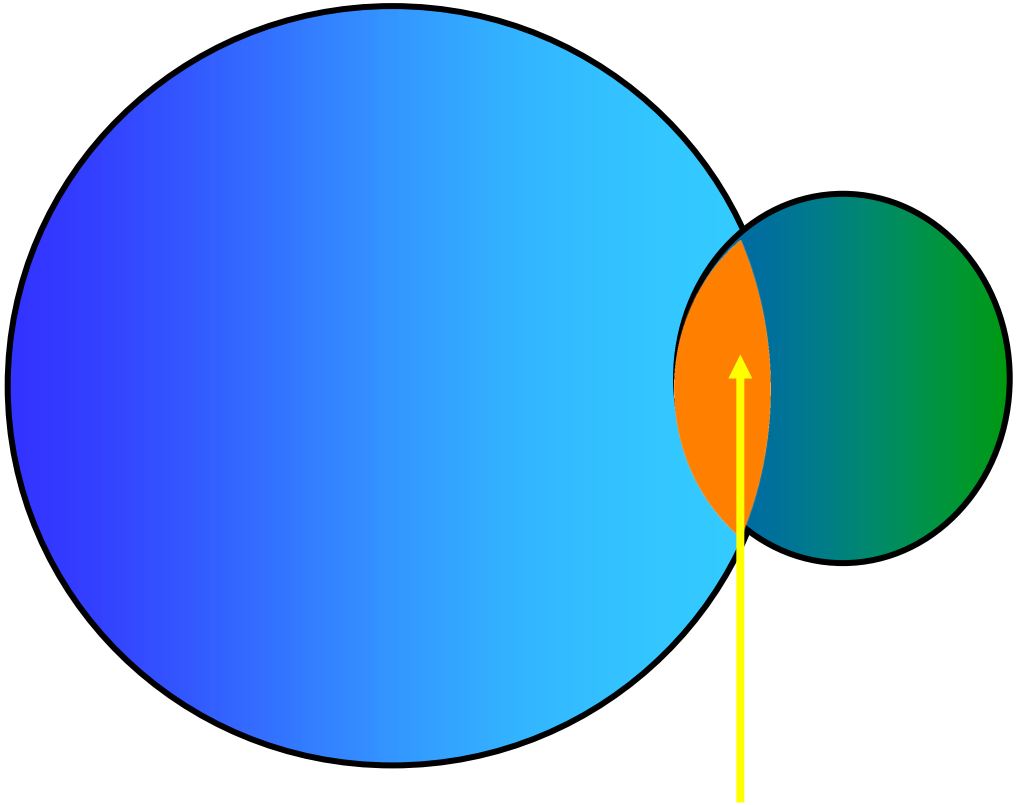
  Gillead

  Abbvie

  Janssen

- Médico Infectologista da SES/SP

Prevalência Global de co-infecção HIV–HCV



1. World Health Organization. *Hepatitis C Fact Sheet No. 164*, October 2000
2. UNAIDS, *AIDS Epidemic Update* 2004

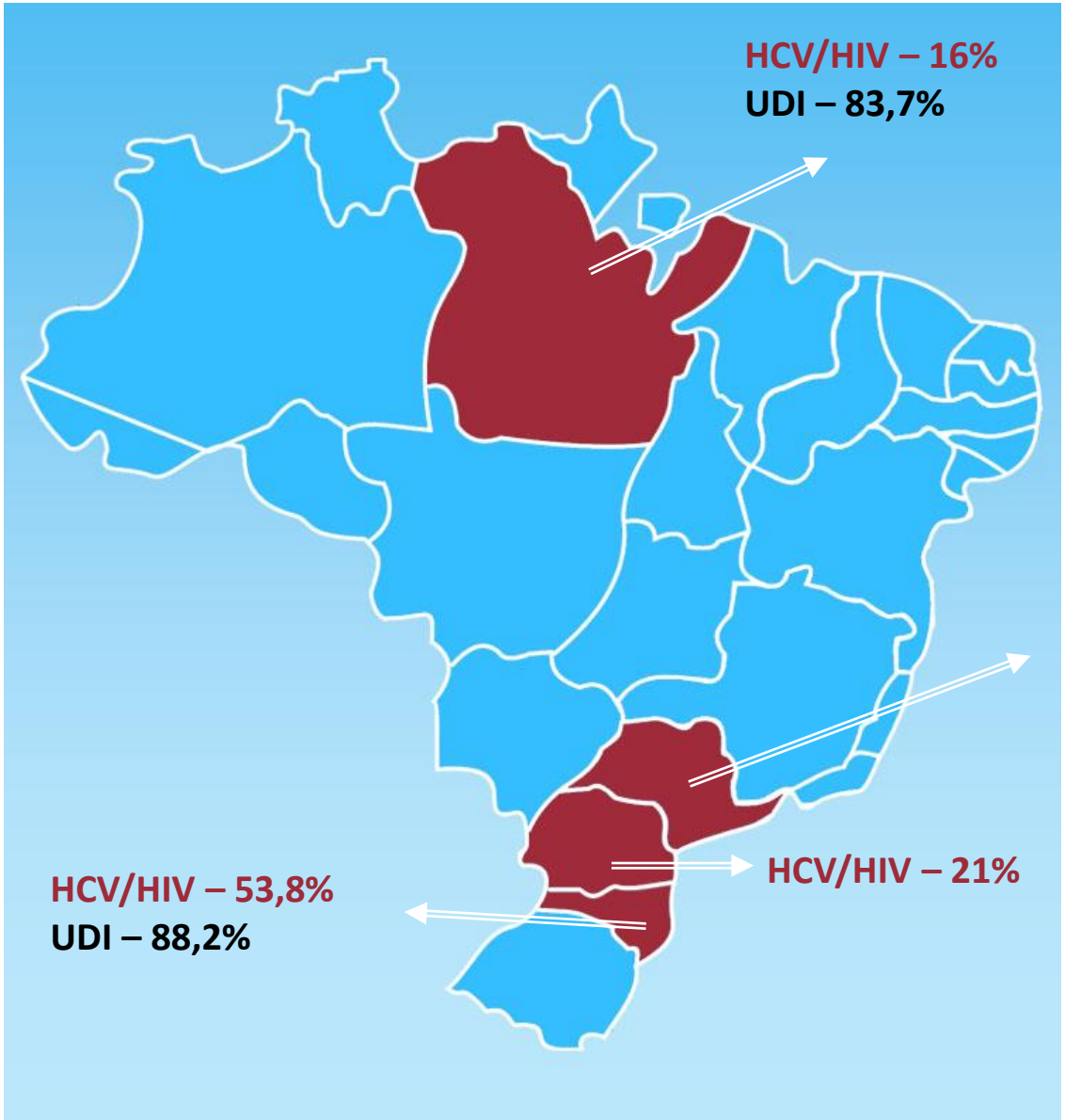
Epidemiologia HIV/HCV

Prevalência do HCV

Na População Soropositiva para HIV	9% - 40%
Em HSH Soropositivos para HIV	4% - 8%
Em Hemofílicos soropositivos para HIV	60% -85%
Usuários de drogas injetáveis Soropositivos para HIV	52% - 90%

Sherman et.al Antiviral Ther 2000

PREVALÊNCIA DA INFECÇÃO PELO HCV EM PORTADORES DO HIV NO BRASIL

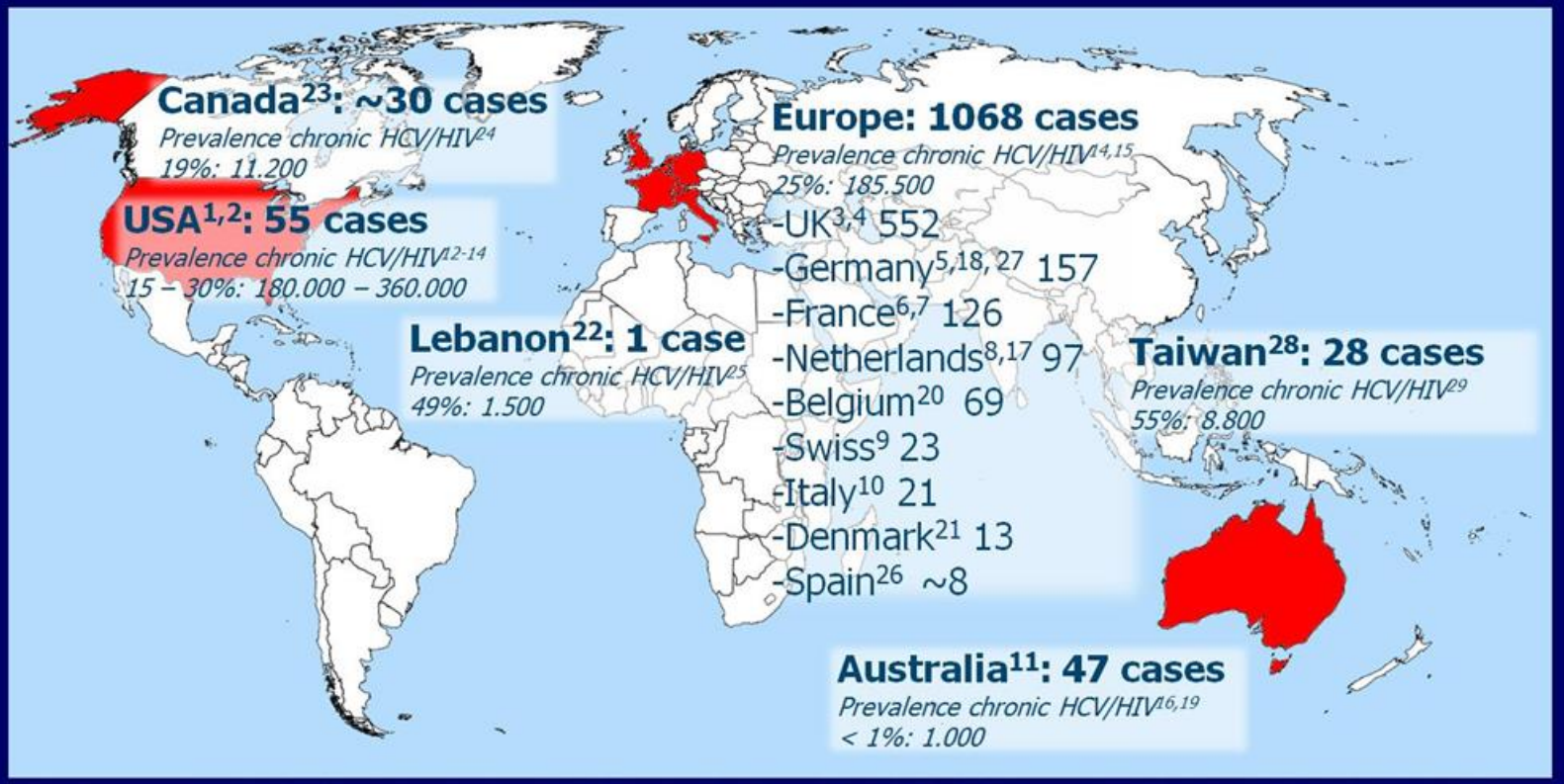


16,0% - 53,8%

SP-Casa da Aids – 17,7%
Campinas – 53,8%
Santos – 36,2%
Santos – 84,8%

1. Monteiro MR., et al., Rev Soc Bras Med Trop. 2004
2. Mendes-Correa., et al., Rev Inst Med Trop SP. 2000
3 Pavan MH. et al., Braz J Infect Dis. 2004
4. Segurado AC. et al., AIDS Patient Care STDS. 2004
5. Vogler IH. Et al., Rev Inst Med Trop SP. 2004
6. Treitinger A. et al., Braz J Infect Dis. 2000

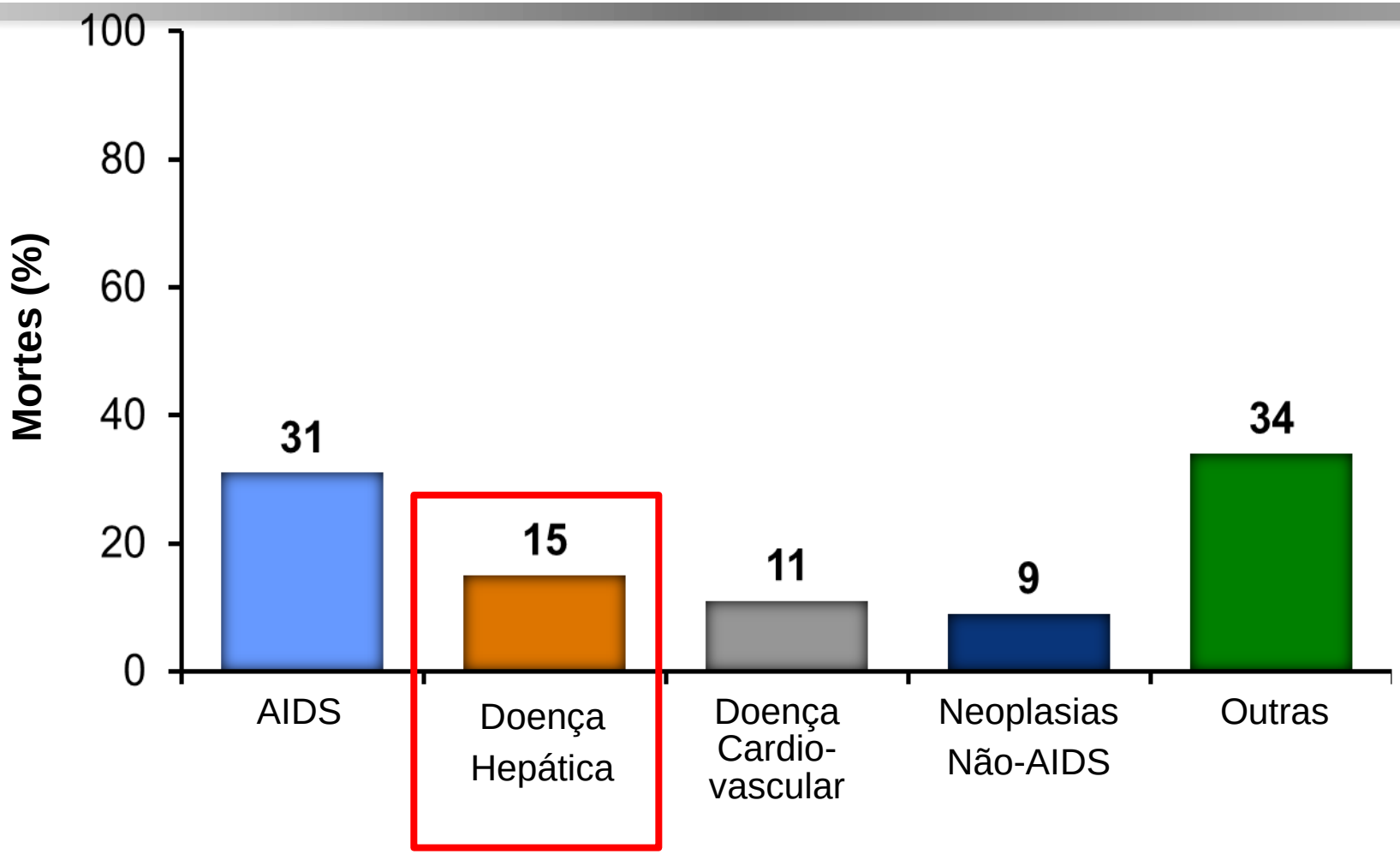
Infecção aguda de HCV entre HSH HIV +



1:Luetkemeyer JAIDS 2006; 2:Cox Gastroenterology 2008; 3:Giraudon Sex Transm Infect 2008; 4:Ruf Eurosurveill 2008; 5:Vogel CID 2009; 6:Gambotti Euro Surveill 2005; 7:Morin Eur J Gastro Hepat 2011; 8:Urbanus AIDS 2009; 9:Rauch CID 2005; 10:Gallotta 4th Works. HIV & Hep. Coinf. 2008; 11:Matthews CID 2009; 12:Sherman CID 2002; 13:Backus JAIDS 2005; 14:UNAIDS Report 2008; 15:Soriano JID 2008; 16:Matthews CID 2011; 17:Arends Neth J Med 2011; 18:Neukam HIV Med 2011; 19:Pfafferott PLoS One 2011; 20:Bottieau Euro Surveill 2010; 21:Barfod Scand JID 2011; 22:Dionne-Odom Lancet Infect Dis 2009; 23:Hull personal conversation 2011; 24:Remis Public Health Agency of Canada 2002; 25:UNGASS Country progress Report 2010; 26:Soriano personal conversation 2011; 27:Boesecke 18thCROI Boston 2011 abstract #113; 28:Sun Liver International 2011; 29:Lee J F Med Assoc 2008

Principal Causa de Morte em Portadores de HIV (n=23,441)
D:A:D Study

15% das 1246 mortes foram relacionadas a doença hepática



Weber R, et al. Arch Intern Med 2006;166:1632–41

HIV/HCV – Duplo Problema para o Fígado

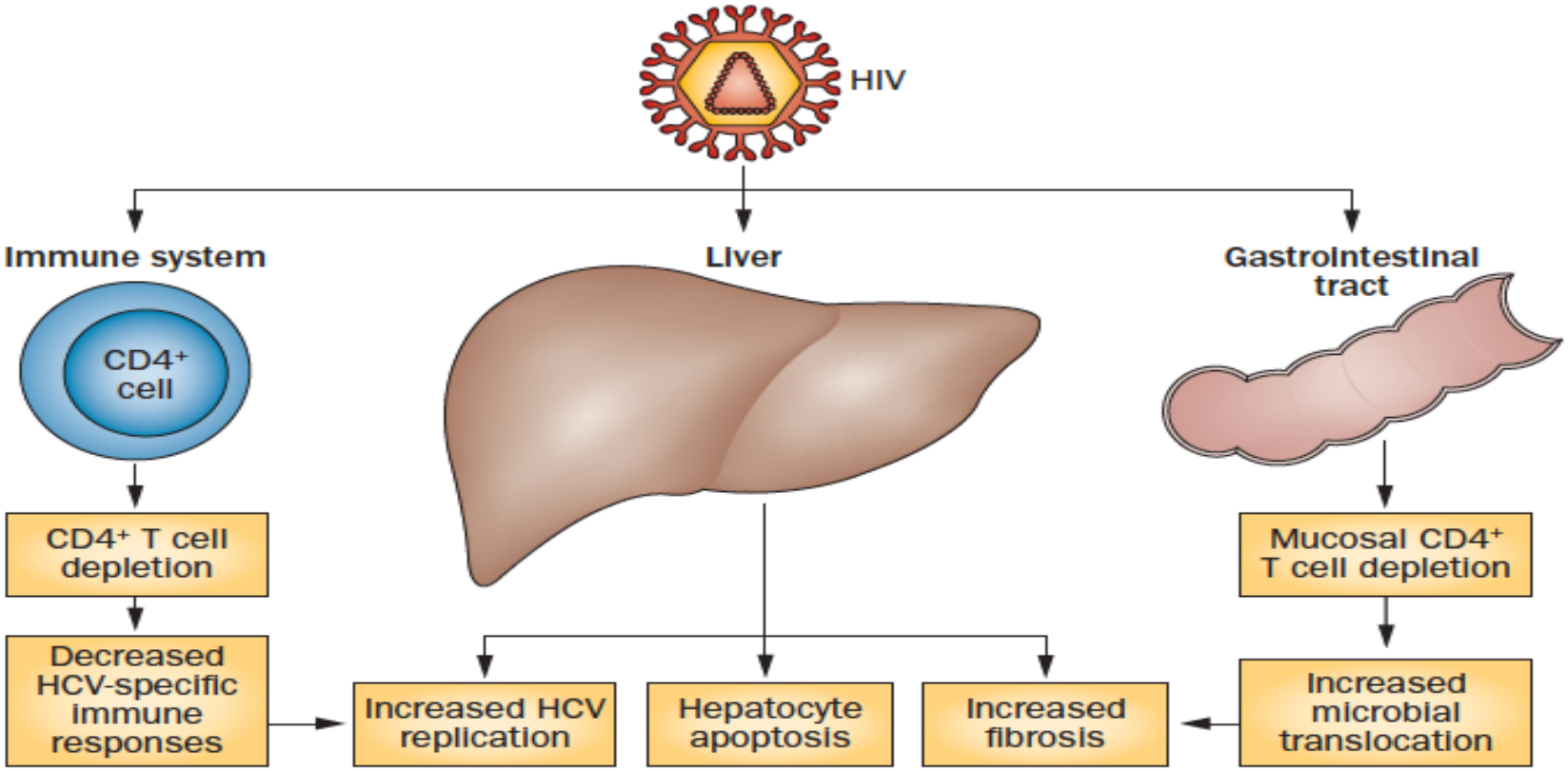
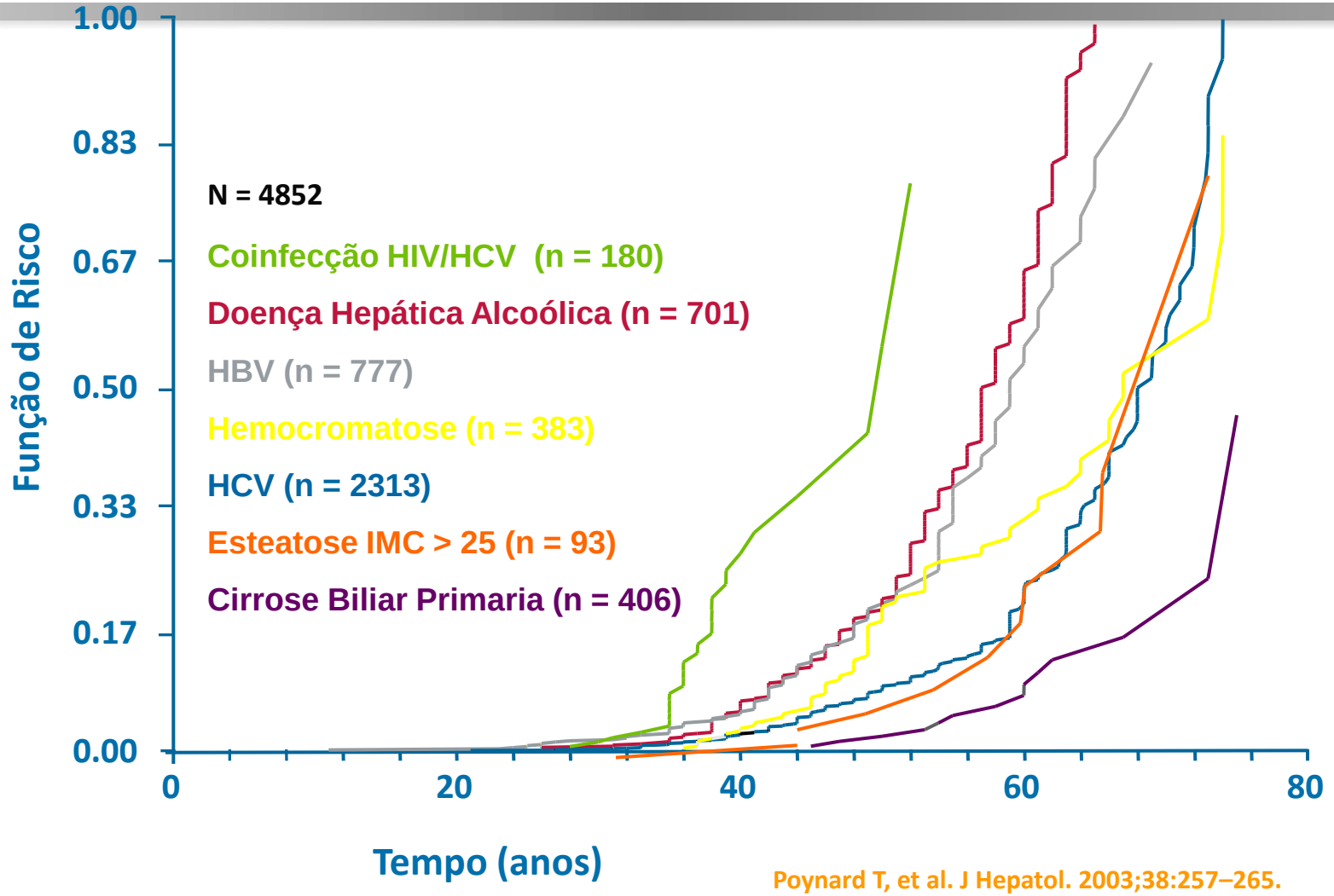


Figure 1 | Driving factors underlying liver disease pathogenesis in HCV–HIV co-infection. HIV infection leads to an impaired immune response against HCV, increased HCV replication, hepatic inflammation and apoptosis, increased microbial translocation from the gastrointestinal tract and increased fibrosis.

Chen J Nat Rev Gastroenterol Hep 2014 doi:10.1038/nrgastro.2014.17

Evolução mais rápida de fibrose hepática em coinfectados HIV/HCV

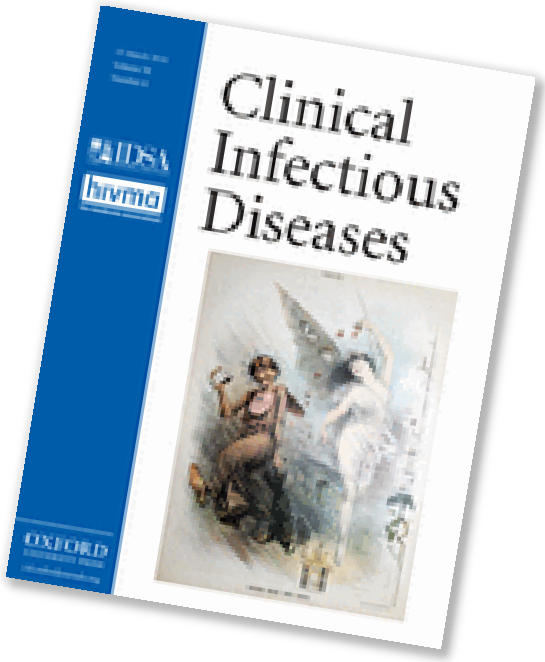


Poynard T, et al. J Hepatol. 2003;38:257–265.

TARV Reduz Descompensação Hepática em Coinfectados HIV-HCV

Objetivo:

- 10.090 homens coinfectados HIV/HCV
- Veterans Aging Cohort Study (USA)
- Virgens de TARV na inclusão
- Incidência de descompensação hepática entre 1996 and 2010

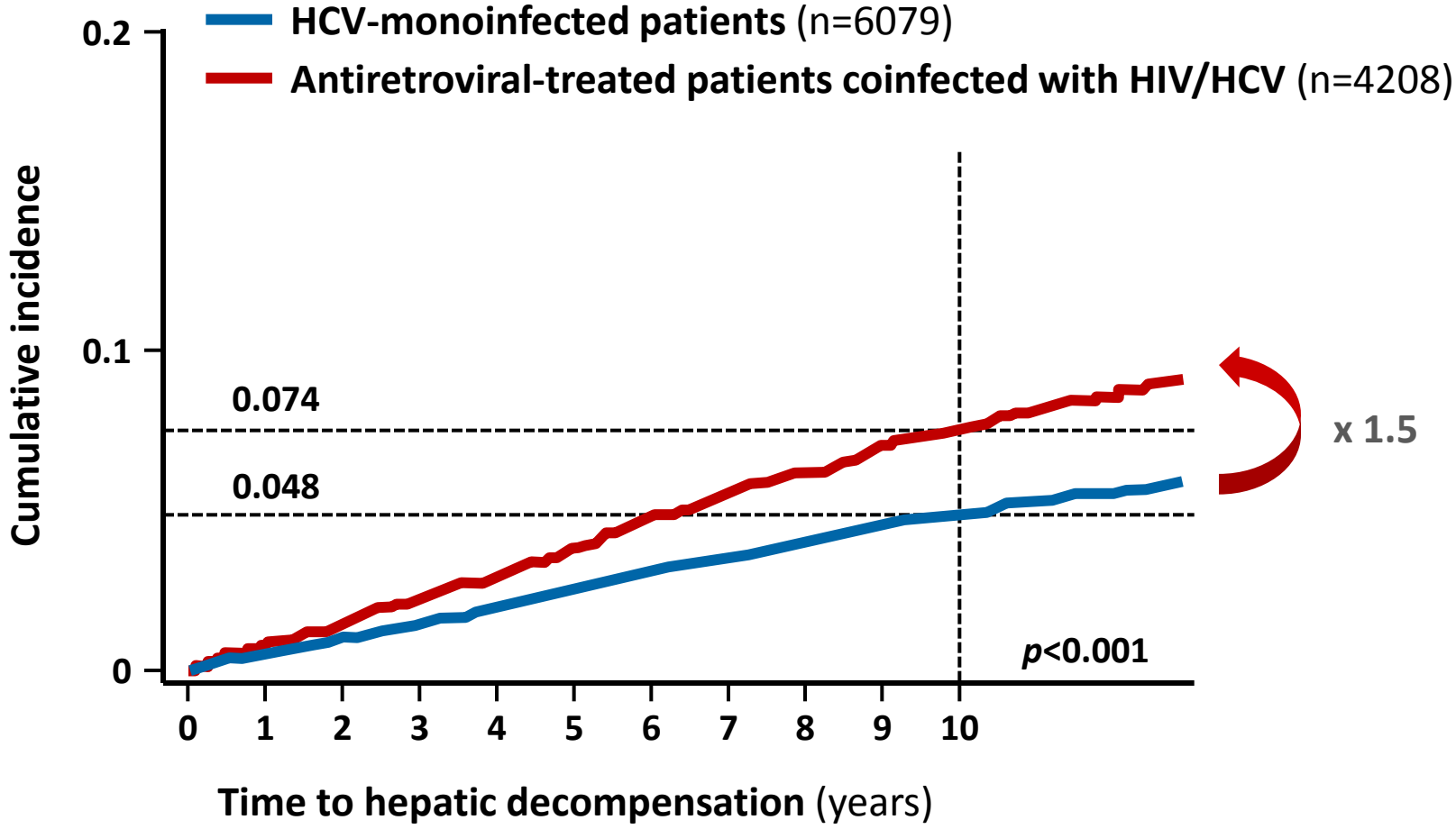


Results:

- Início do TARV reduziu de forma significante a taxa de descompensação hepatica em 28–41% na média

Anderson JP, et al. Clin Infect Dis 2014; 58(5): 719–27.

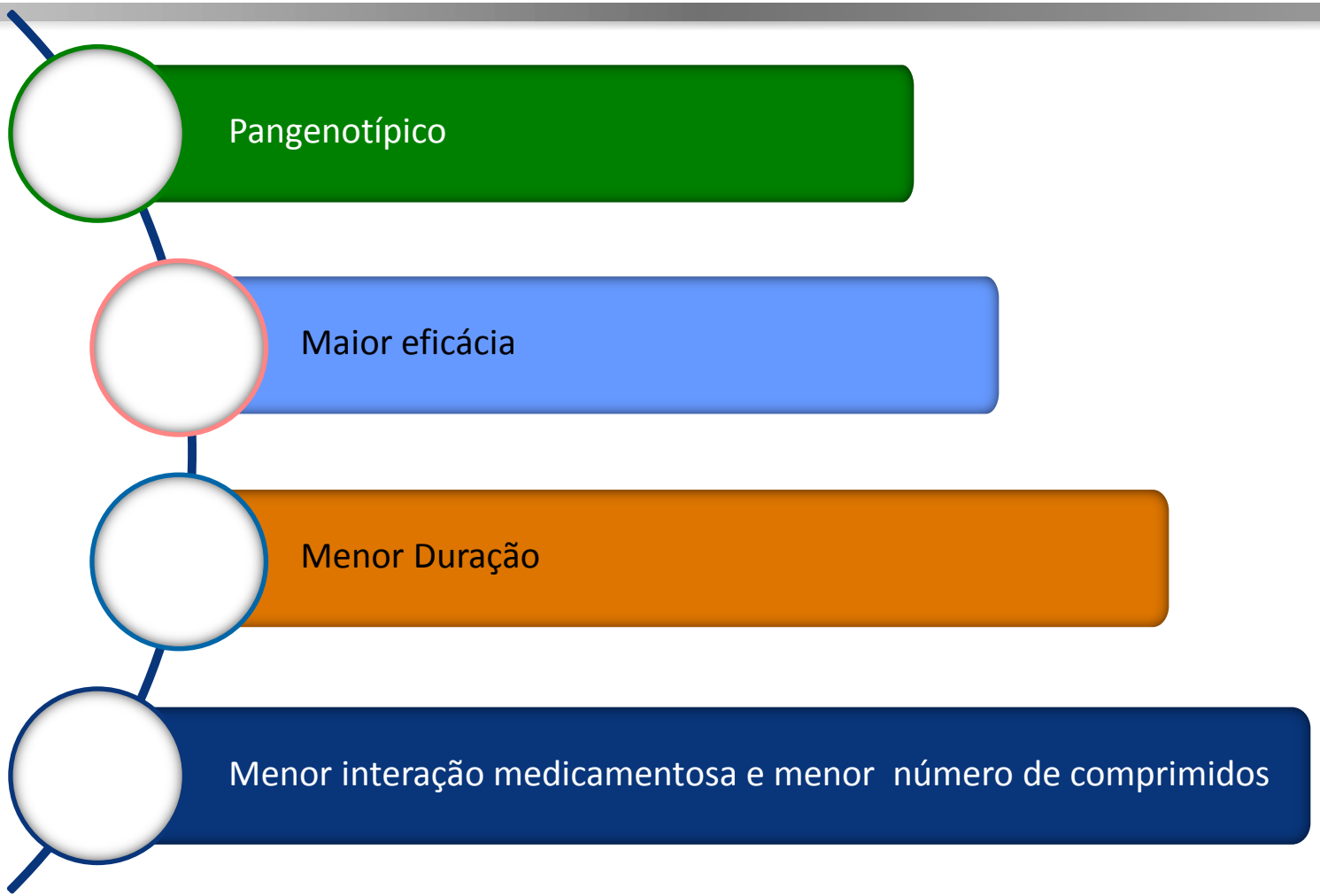
A Progressão da Hepatopatia pelo HCV Continua mais Rápida em Coinfectados pelo HIV a Despeito de TARV Efetivo



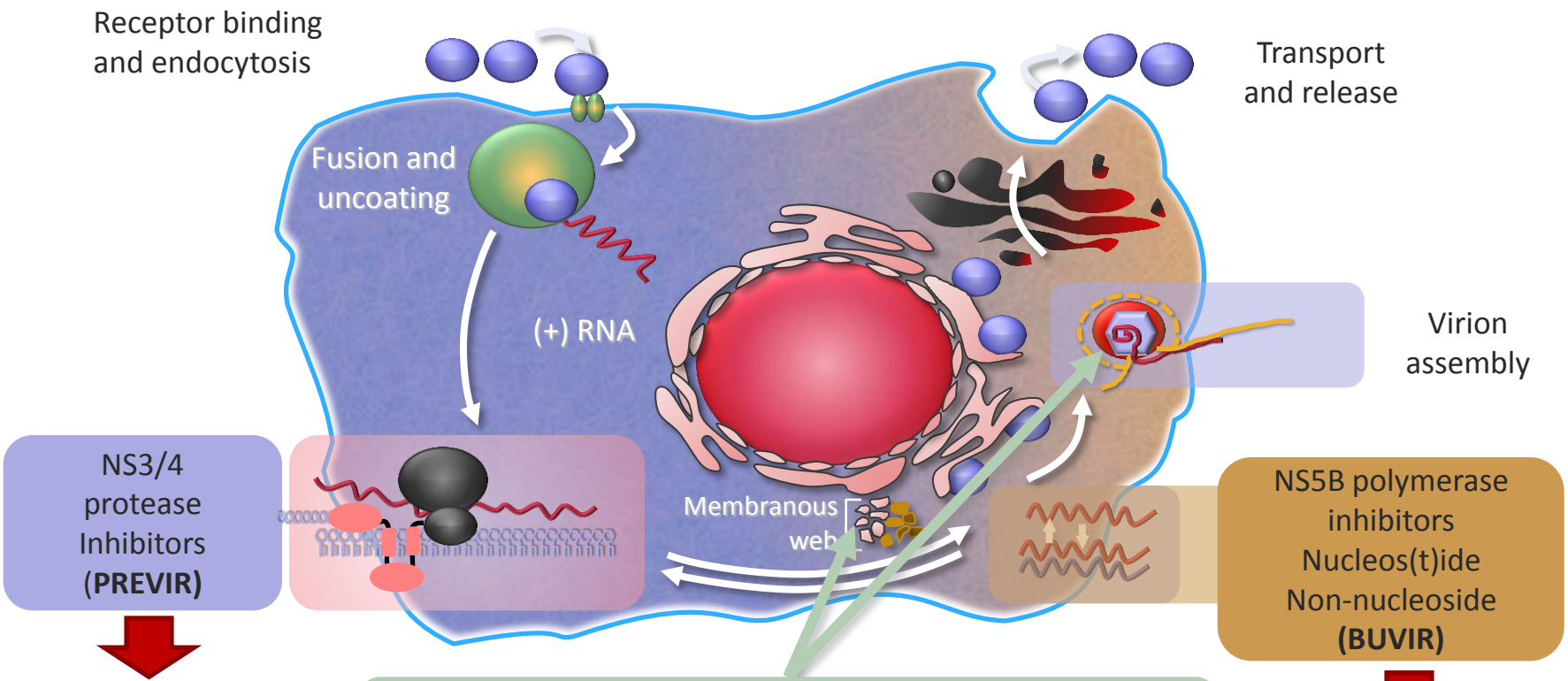
ART, antiretroviral therapy

Adapted from: Lo Re 3rd V, et al. Ann Intern Med 2014;160:369–79.

E na Era “Interferon Free”, quais as melhores qualidades de um esquema de tratamento?



ALVOS PARA AÇÃO DOS DAA CONTRA O HCV



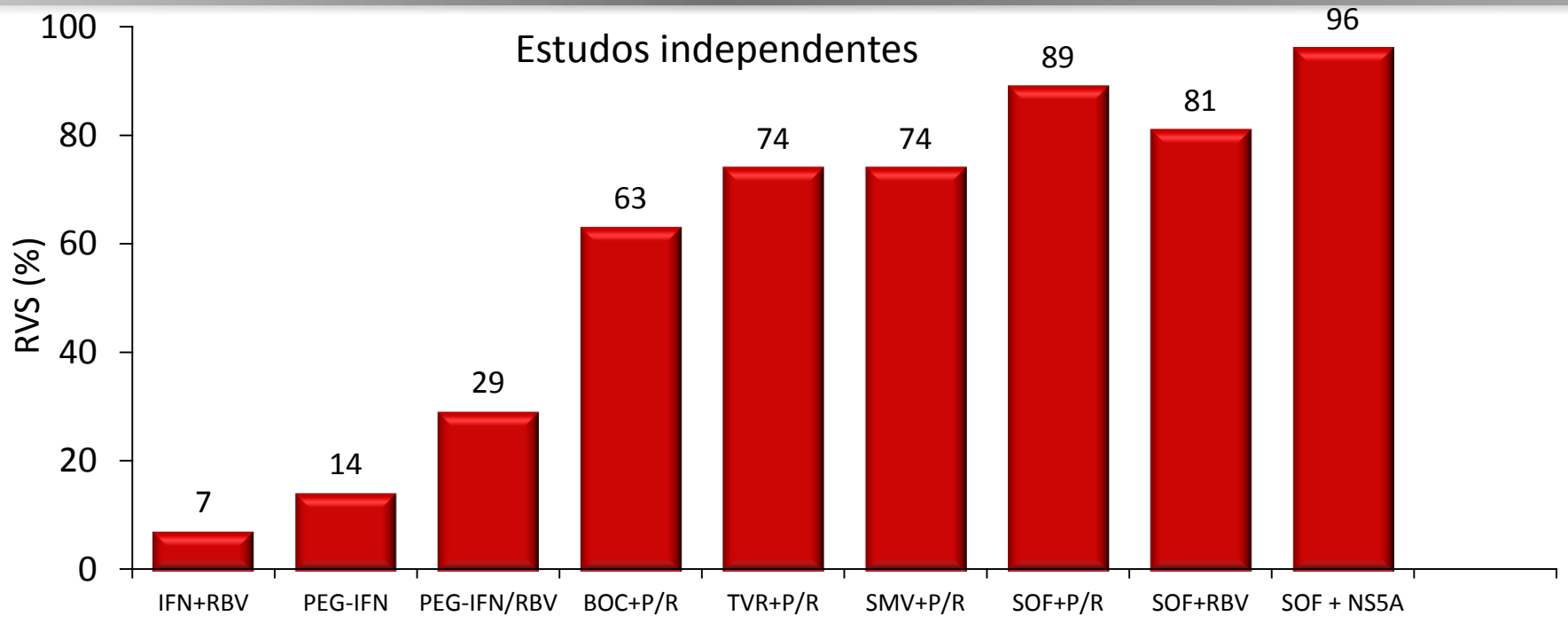
Boceprevir
Telaprevir
Simeprevir
Asunaprevir
Veruprevir/r
Grazoprevir

Daclatasvir, Ledipasvir, Ombitasvir, Elbasvir

Sofosbuvir
Dasabuvir
Beclabuvir

Adaptado de Manns MP, et al. *Nat Rev Drug Discov*. 2007;6:991-1000.

Melhora das Taxas de RVS12/24 ao Longo do Tempo em Pacientes Coinfectados HIV-HCV GT1

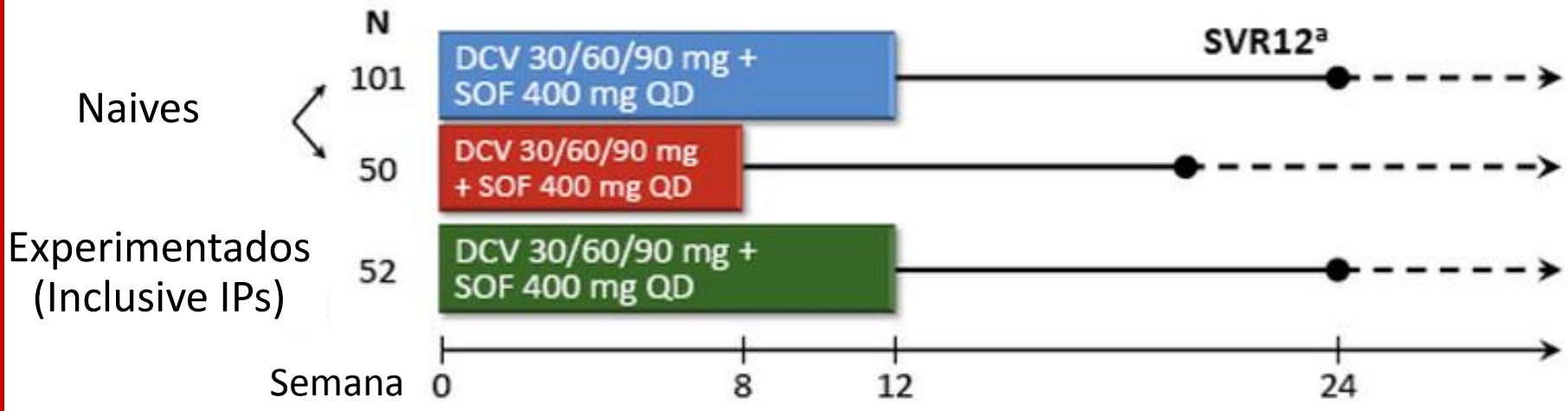


NA ERA DOS DAA PACIENTES HIV+ VÃO ATINGIR TAXAS SEMELHANTES DE RVS

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

BOC, boceprevir;
DAA, direct-acting antiviral agent; P/R, pegylated interferon/ribavirin;
SMV, simeprevir; SOF, sofosbuvir; TVR, telaprevir

Estudo ALLY-2 (Fase 3) – HCV/HIV: SOF + DCV por 8 a 12 semanas



- **Dose do Daclatasvir**: 60mg/dia, ajustada de acordo com TARV:
  - 30 mg para IPs com ritonavir e 90 mg para Inib. TR não-nuc (INNRT).
- **Pacientes do estudo**: 34% negros, 14% Cirróticos, 83% GT1

Wyles DL, et al. NEJM 2015, Jul 21

Estudo ALLY-2 (Fase 3) – HCV/HIV: SOF + DCV por 8 a 12 semanas

Table 3. Baseline HIV Disease Characteristics and ARV Regimens

Parameter	Treatment-naive 12 weeks treatment N = 101	Treatment-naive 8 weeks treatment N = 50	Treatment-experienced 12 weeks treatment N = 52
HIV RNA <50 copies/mL, n/m (%)[a]	94/100 (94.0)	45/48 (93.8)	47/49 (95.9)
CD4 cells per mm³, median (range)	520 (122–1147)	575 (157–1430)	636 (262–1470)
HIV treatment, n (%)[b]	100 (99.0)	48 (96.0)	51 (98.1)
Darunavir/r	19/100 (19.0)	21/48 (43.8)	11/51 (21.6)
Atazanavir/r	19/100 (19.0)	5/48 (10.4)	12/51 (23.5)
Lopinavir/r	9/100 (9.0)	3/48 (6.3)	0
Efavirenz	18/100 (18.0)	8/48 (16.7)	8/51 (15.7)
Nevirapine	5/100 (5.0)	1/48 (2.1)	3/51 (5.9)
Rilpivirine	5/100 (5.0)	1/48 (2.1)	1/51 (2.0)
Raltegravir	22/100 (22.0)	8/48 (16.7)	10/51 (19.6)
Dolutegravir	3/100 (3.0)	1/48 (2.1)	4/51 (7.8)
Nucleosides only	0	0	2/51 (3.9)

[a] Patients on antiretroviral therapy with available baseline HIV RNA data.
[b] Nucleoside analogs in regimen not listed.

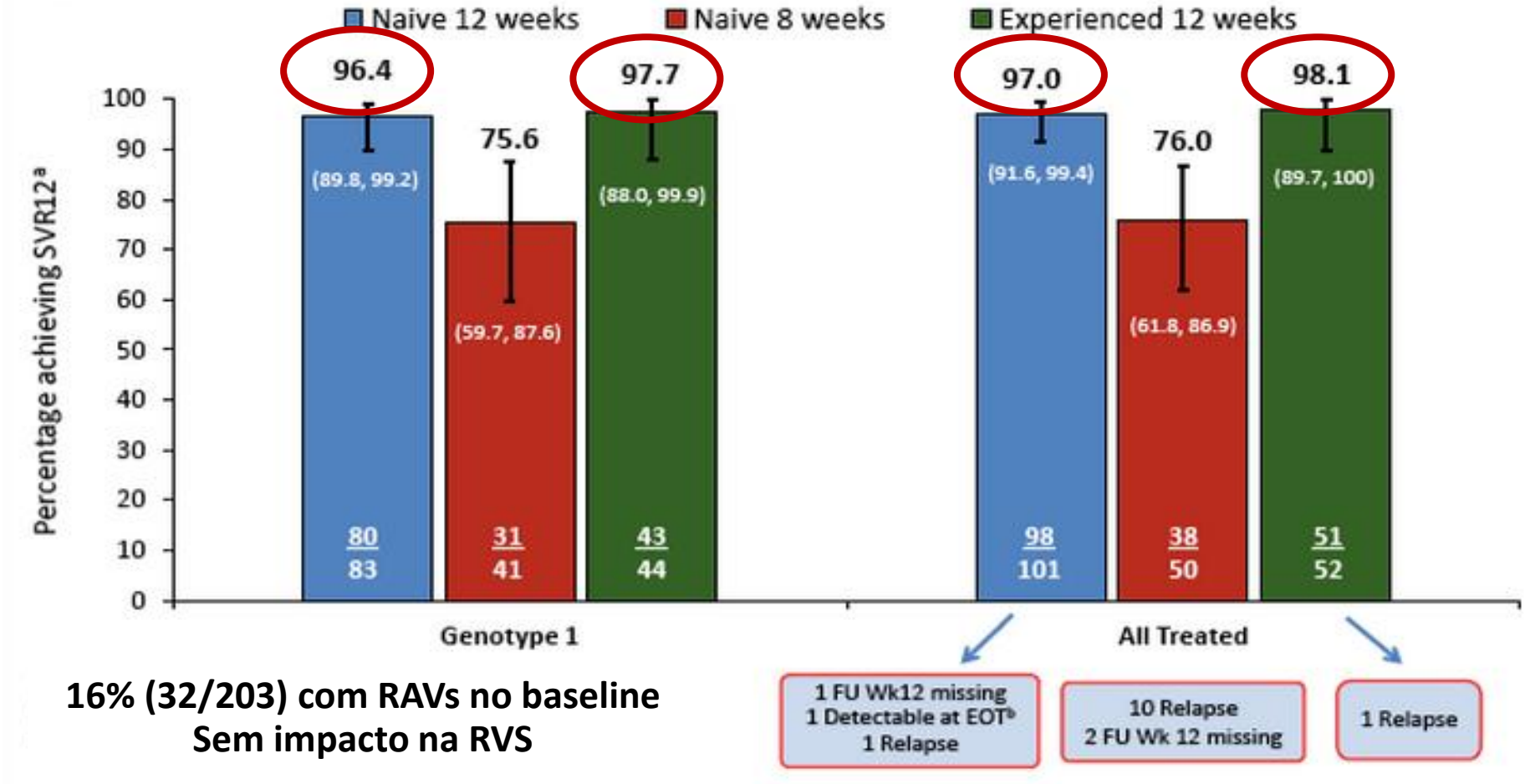
- Four patients (2.0%) were not receiving cART

Wyles DL, et al. NEJM 2015, Jul 21

Estudo ALLY-2 (Fase 3) – HCV/HIV: SOF + DCV por 8 a 12 semanas

	ALLY-2	ION-4[6]	Turquoise-1[7,a]
Atazanavir/r	✓		✓
Darunavir/r	✓		
Lopinavir/r	✓		
Efavirenz	✓	✓	
Nevirapine	✓		
Rilpivirine	✓	✓	
Dolutegravir	✓		
Raltegravir	✓	✓	✓
Enfuvirtide	✓		
Maraviroc	✓		
Zidovudine	✓		
Lamivudine	✓		✓
Abacavir	✓		
Tenofovir	✓	✓	✓
Emtricitabine	✓	✓	✓

Estudo ALLY-2 (Fase 3) – HCV/HIV: SOF + DCV por 8 a 12 semanas

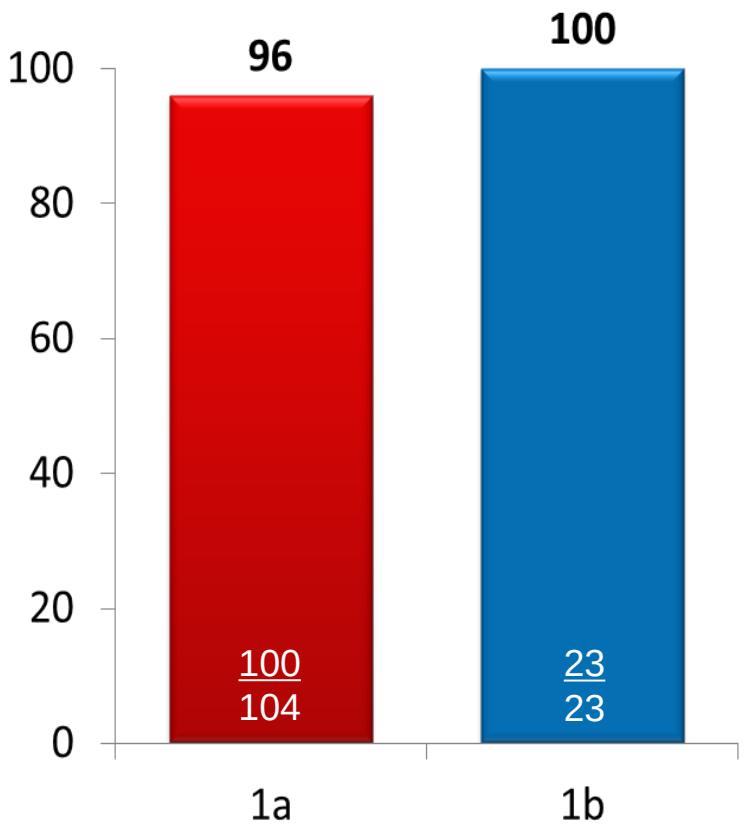


16% (32/203) com RAVs no baseline
Sem impacto na RVS

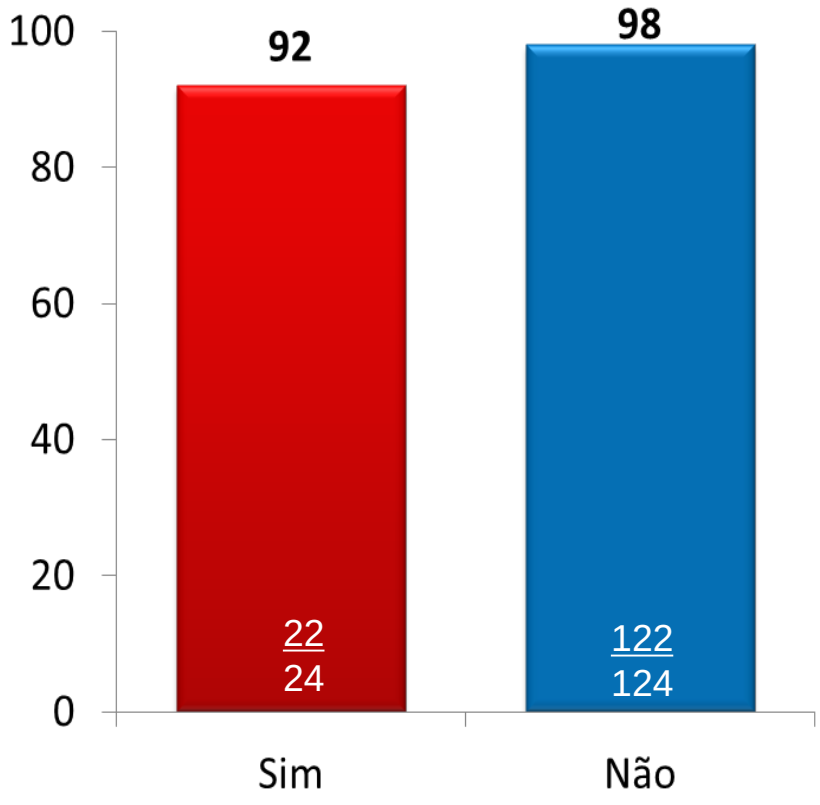
Wyles DL, et al. NEJM 2015, Jul 21

Estudo ALLY-2 (Fase 3): HCV/HIV: **SOF + DCV** 12 semanas

Genótipo



Cirrose



Wyles DL, et al. NEJM 2015, Jul 21

Estudo ALLY-2 (Fase 3) – HCV/HIV: SOF + DCV por 12 semanas

Table 4. Summary of Adverse Events During Treatment

Event, n (%)	Treatment-naive 12 weeks treatment N = 101	Treatment-naive 8 weeks treatment N = 50	Treatment-experienced 12 weeks treatment N = 52
Patients with at least one AE	74 (73.3)	29 (58.0)	37 (71.2)
Serious AEs[a]	1 (1.0)	0	3 (5.8)
Death[b]	0	1 (2.0)	0
Grade 3-4 AEs	2 (2.0)	2 (4.0)	4 (7.7)
Discontinuations for AEs	0	0	0
Common AEs on treatment (≥ 10% in any treatment group)			
Fatigue	19 (18.8)	5 (10.0)	10 (19.2)
Nausea	14 (13.9)	4 (8.0)	8 (15.4)
Headache	12 (11.9)	3 (6.0)	8 (15.4)
Diarrhea	11 (10.9)	1 (2.0)	3 (5.8)
Treatment-emergent grade 3–4 laboratory abnormalities[c]			
INR ≥ 2.1×ULN	1 (1)	0	1 (1.9)
AST ≥ 5.1×ULN	0	1 (2.0)	0
Total bilirubin ≥ 2.6×ULN[d]	5 (5.0)	1 (2.0)	2 (3.8)
Lipase ≥ 3.1×ULN[e]	5 (5.0)	1 (2.0)	1 (1.9)

[a] Serious AEs: Priapism, chest pain/presyncope, drug abuse/pulmonary embolism, and hypertensive crisis/syncope, all unrelated to treatment (1 patient each).
[b] Includes pretreatment, on-treatment and during posttreatment follow-up: 52 year old male with cardiac arrest at posttreatment week 4, unrelated to study therapy.
[c] No grade 3–4 ALT elevations were detected; all grade 3–4 laboratory abnormalities are listed.
[d] All patients were receiving concomitant atazanavir-ritonavir.
[e] Transient hyperlipasemia without reported pancreatitis.

Wyles DL, et al. NEJM 2015, Jul 21

Estudo “Vida real”

- France - ATU

DACLATASVIR PLUS SOFOSBUVIR WITH OR WITHOUT RIBAVIRIN IN PATIENTS WITH HIV-HCV COINFECTION: INTERIM ANALYSIS OF A FRENCH MULTICENTER COMPASSIONATE USE PROGRAM

Hélène Fontaine* [1], Karine Lacombe[2], Catherine Dhiver[3], Eric Rosenthal[4], Sophie Metivier[5], Teresa Antonini-Michelle[6], Marc Antoine Valantin[7], Laurent Cotte[8], Julie Botero[9], Stanislas Harent[10], Dominique Batisse[11], Georges-Philippe Pageaux[12], Hugues Aumaitre[13], Stephanie Dominguez[14], Victor De Ledinghen[15], Vincent Leroy[16], Francois Dabis[17], Linda Wittkop[17], Anne Filipovics[18], Marie Helene Barlet[18], Yacia Bennai[18], Dominique Salmon[19] on behalf of Bristol-Myers Squibb and ANRS CO13-HEPAVIH Cohort

[1]Hôpital Cochin, [2]Hôpital St Antoine, Service de Maladies Infectieuses, Paris, [3]Centre Hospitalo-Universitaire Conception, Assistance Publique-Hôpitaux de Marseille, Marseille, [4]Hôpital Archet, CHU de Nice, Nice, [5]Pôle Digestif-Gastroentérologie-Hépatologie, CHU Purpan, Toulouse, [6]AP-HP Hôpital Paul-Brousse, Centre Hépato-Biliaire, Villejuif, [7]AP-HP, Hôpital Pitié Salpêtrière, Service de Maladies infectieuses et tropicales, Paris, [8]Service des Maladies infectieuses et tropicales, Hospices Civils de Lyon, Lyon, [9]AP-HP, Hôpital St Antoine, Service de Maladies Infectieuses, [10]Service de Maladies Infectieuses et Tropicales, Hôpital Bichat-Claude Bernard , [11]AP-HP, Georges Pompidou European Hospital, Paris, [12]CHU Saint-Eloi, Montpellier, 13Saint-Jean Hospital, Perpignan, [14]Henri Mondor Hospital, Créteil, [15]Centre d'Investigation de la Fibrose hépatique, Hôpital Haut-Lévêque, Centre Hospitalo-Universitaire de Bordeaux, Pessac, [16]CHU de Grenoble, Clinique universitaire d'hépato-gastroentérologie, Grenoble, [17]Centre INSERM U897-Epidemiologie-Biostatistique & CHU de Bordeaux, Bordeaux, [18]Bristol-Myers Squibb Research and Development, Rueil-Malmaison, [19]Médecine interne et maladies infectieuses, Hôpital Cochin, Paris, France

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APRIL 22-26, VIENNA, AUSTRIA

Caracteristicas Baseline

Parameter	All Patients (N = 727)*
Age, median years (range)	52.3 (27-74)
Sex ratio, M/F	2.62
Fibrosis stage, n	
F0–F2	36
F3[a]	164
F4	508
Child-Pugh class B/C among patients with F4	81
Treatment experienced	573
CD4 cells/mm^3, mean (SD)	591 (348)
HIV viremia, n (%)[b]	
Undetectable	649 (98)
Detectable	12 (2)
< 200 copies/mL	600 (98)
≥ 200 copies/mL	12 (2)
Copies/mL: patients with detectable HIV, mean (SD)[c]	32,246 (70,777)

[a] Includes F3 and F3/F4.
[b] 66 patients had missing data.
[c] 115 patients had missing data.

Fontaine H, *et al.* EASL 2015; Poster LP23.

Vida Real França (ANRS): GT1, 3 e 4 HCV/HIV

SOF+DCV±RBV por 12 ou 24 semanas

- **n = 147** pacientes com 12 semanas pós-tto: interim

  70% GT1; 10% GT3; 20% GT4

  > 75% F4

  > 85% experimentados

  13% **Child B/C**

  Pctes pré e pós TxH, pré Tx Renal

  Análise de segurança em 564 pctes incluídos.

- **Tratamento**: 12s em 31% e 24s em 68%; RBV em 9%

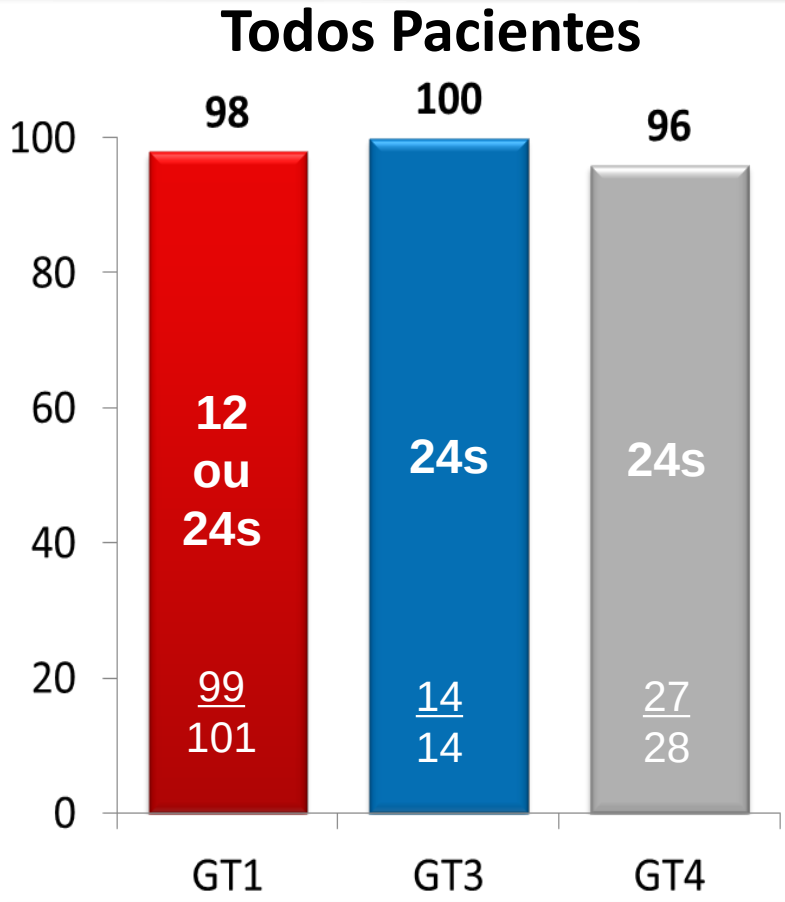
  97% dos pctes em TARV

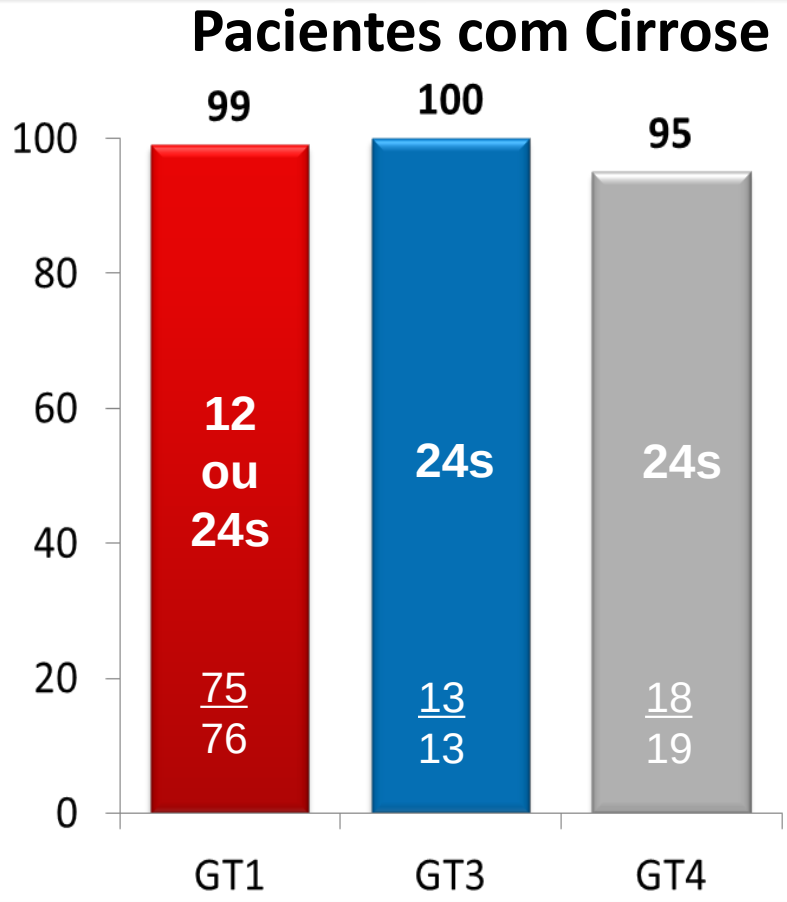
- **Dose do Daclatasvir**: 60mg/dia, de acordo com TARV

Lacombe K, et al. IAS 2015

Vida Real Francês: SOF+DCV±RBV 12/24s

Resultados apenas dos pacientes com seguimento de 12s Pós-Tto





GT1 F4	**SOF+DCV:**	**12s=100% (n=15/15)**	**24s, 98% (n=52/53)**
	SOF+DCV+RBV:	**12s=100% (n=3/3);**	**24s, 100%(n=4/4)**

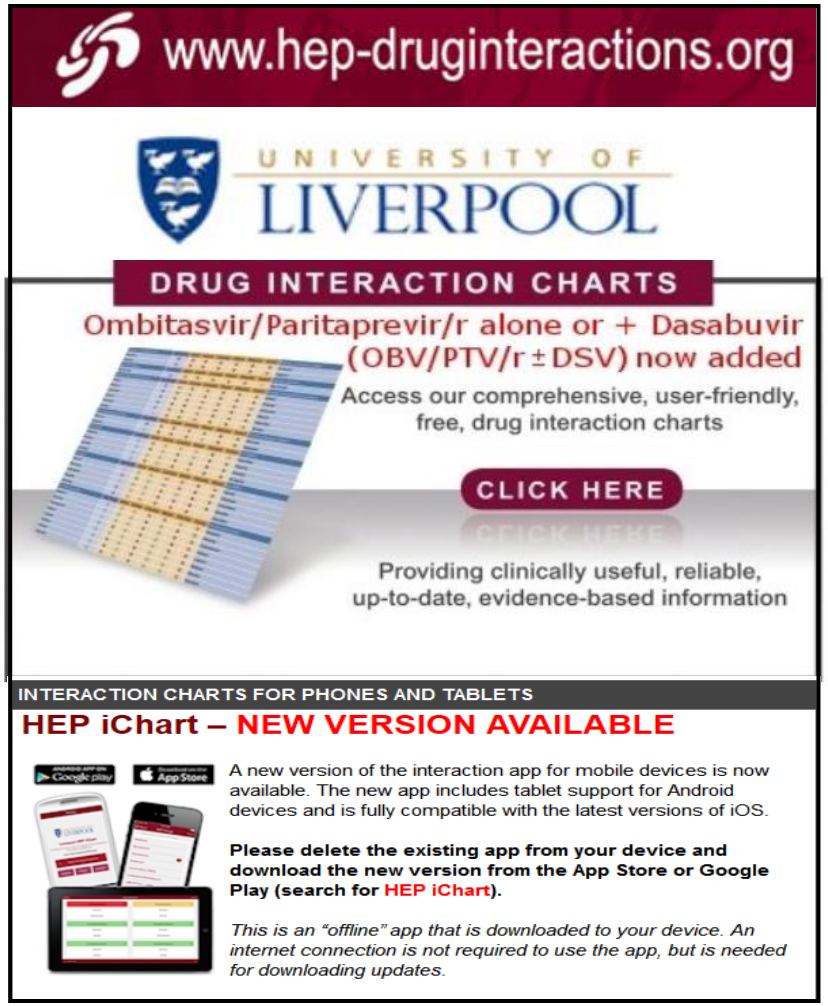
Lacombe K, et al. IAS 2015

Interações Medicamentosas DAA e TARV

EASL Guideline, 2015

		SIM	DCV	SOF	SOF/ LDV	3D
NRTIs	Abacavir	•	•	•	•	•
	Didanosine	•	•	•	•	•
	Emtricitabine	•	•	•	•	•
	Lamivudine	•	•	•	•	•
	Stavudine	•	•	•	•	•
	Tenofovir	•	•	•	•	•
	Zidovudine	•	•	•	•	•
NNRTIs	Efavirenz	•	90mg	•	•*	•
	Etravirine	•	•	•	•	•
	Nevirapine	•	•	•	•	•
	Rilpivirine	•	•	•	•*	•
Protease inhibitors	Atazanavir; atazanavir/ritonavir	•	30mg	•	•*	•
	Darunavir/ritonavir; darunavir/cobicistat	•	•	•	•*	•
	Fosamprenavir	•	•	•	•*	•
	Lopinavir	•	•	•	•*	•
	Saquinavir	•	•	•	•*	•
Entry/ Integrase inhibitors	Dolutegravir	•	•	•	•	•
	Elvitegravir/cobicistat	•	•	•	•*	•
	Maraviroc	•	•	•	•	•
	Raltegravir	•	•	•	•	•

HEP-DRUG Interactions



Troca Segura dos Antirretrovirais

- Saber histórico de uso e falhas aos antirretrovirais.
- Saber resultados de genotipagens e teste de tropismo prévios e atuais.
- Saber a opinião do médico de referência em genotipagem do HIV (MRG) quanto a barreira genética do esquema a ser proposto.
- Adesão aos antirretrovirais e HIV RNA atual indetectável antes da troca.
- Quanto mais tempo de HIV RNA indetectável antes da troca, mais seguro.
- Pensar sobre o potencial de hepatotoxicidade, alterações metabólicas e interações medicamentosas com o futuro esquema antirretroviral.

Martinez E et al.. AIDS 2010 Jul 17;24(11):1697-707
Eron JJ et al.. Lancet 2010 Jan 30;375(9712):396-407
PCDT HIV, Ministério da Saúde, 2013

PCDT coinfecção HCV-HIV

Genótipo 1	Regime Terapêutico	Tempo
Monoinfecção HCV	*Sofosbuvir+Simeprevir**	*12 semanas*
Monoinfecção HCV (alternativa)	*Sofosbuvir+Daclatasvir**	*12 semanas*
Experimentado com BOC/TEL ou Coinfecção HCV/HIV	*Sofosbuvir+Daclatasvir**	*24 semanas*

- Atenção às interações entre os esquemas DAA e TARV

AJUSTE POSOLÓGICO:

- ✓ DCV com alguns ARV será regulamentado conforme nota técnica a partir do registro da apresentação de 30mg do daclatasvir
- ✓ Tempo de 24 sem: visa atender exigencias da bula mas há evidencias mais recentes que corroboram a possibilidade de reduzir o tempo para 12 semanas

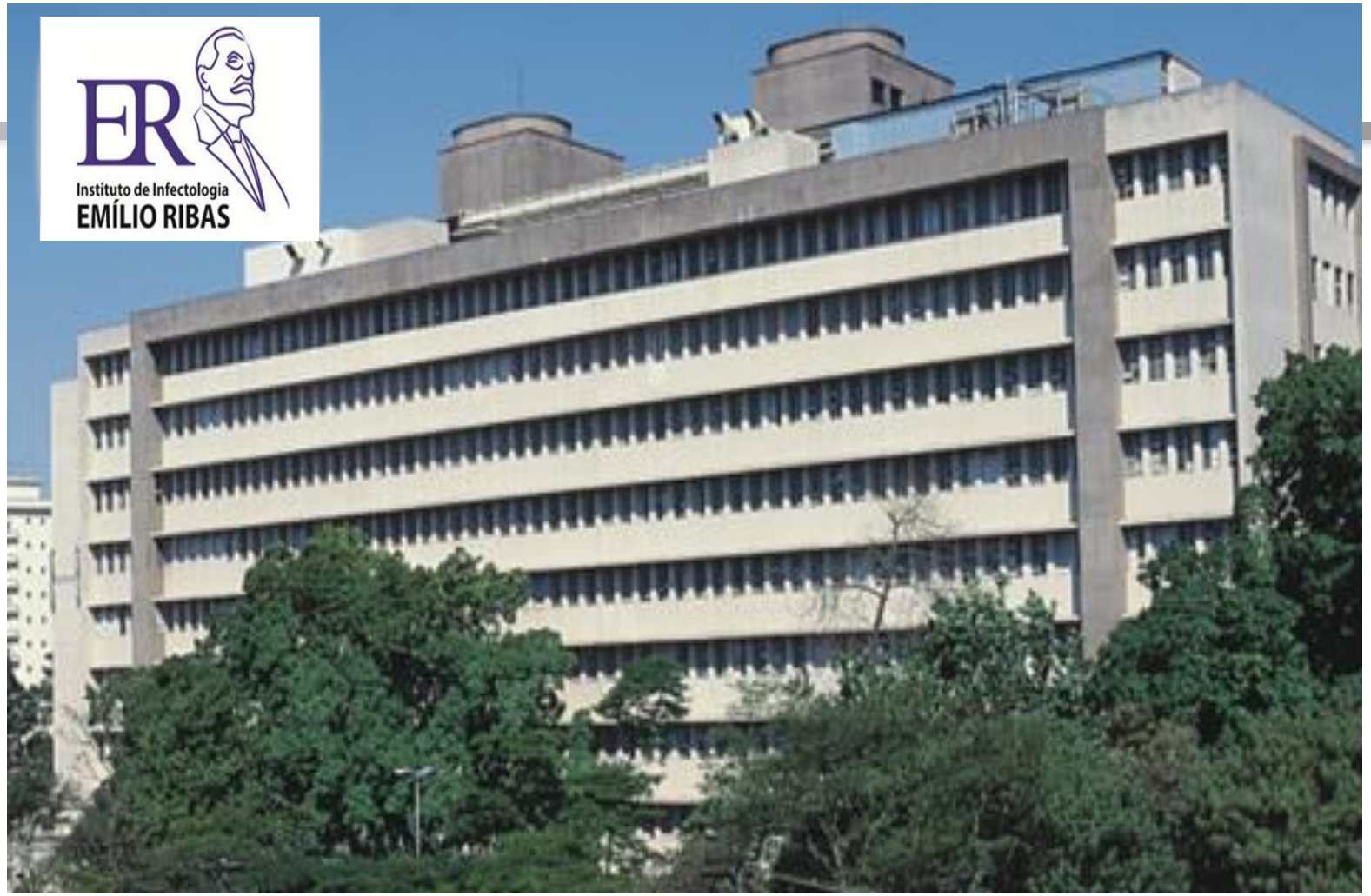
Min Saúde, PCDT 2015

Conclusões

- Evidências apontam para:
  - ✓ SOF+DCV 12s
  - ✓ SOF+DCV+RBV 12s ou sem RBV 24s (cirrose?)

- **Todos** pacientes **devem ser tratados**, independentemente da fibrose ou genótipo.
- **Resultados semelhantes aos pacientes monoinfectados**
- Há esquemas com poucas interações medicamentosas
- Perfil de segurança: favorável em todos os subgrupos

NÚCLEO DE HEPATITES VIRAIS DO IIER



GRATO!

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