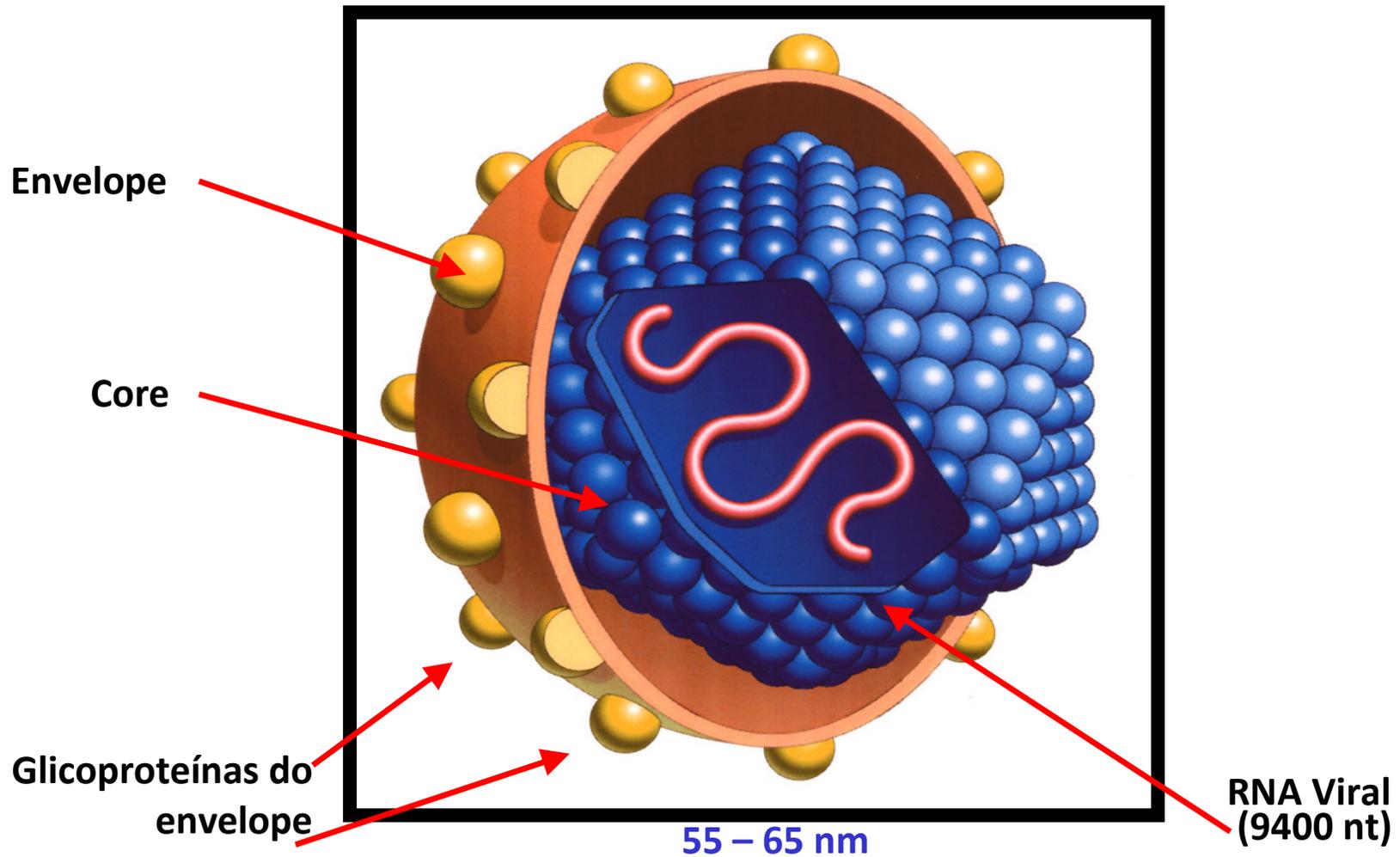


Antivirais de Ação Direta (DAA's)

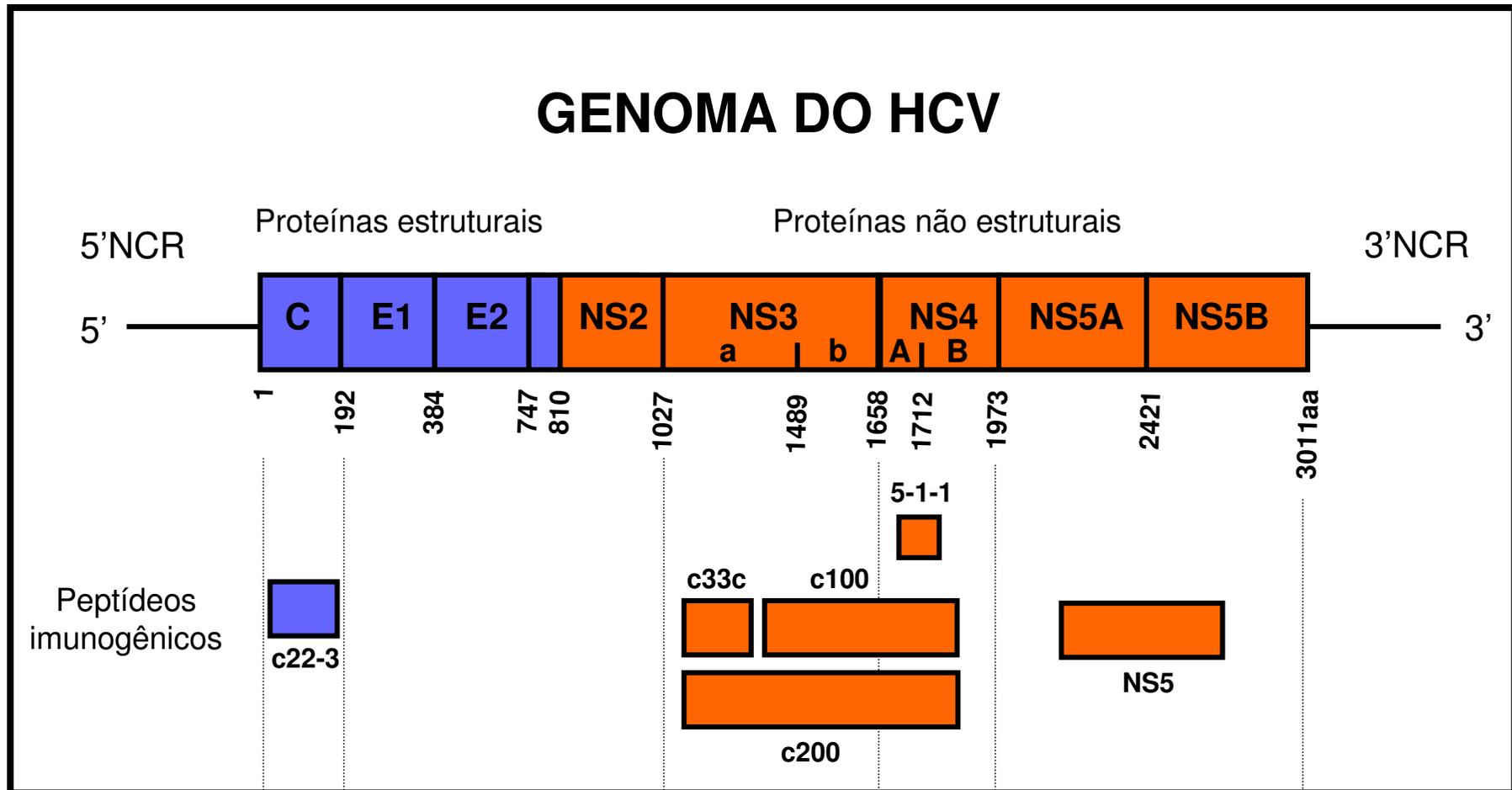
MANEJO DOS PACIENTES PARA EVITAR RESISTÊNCIA

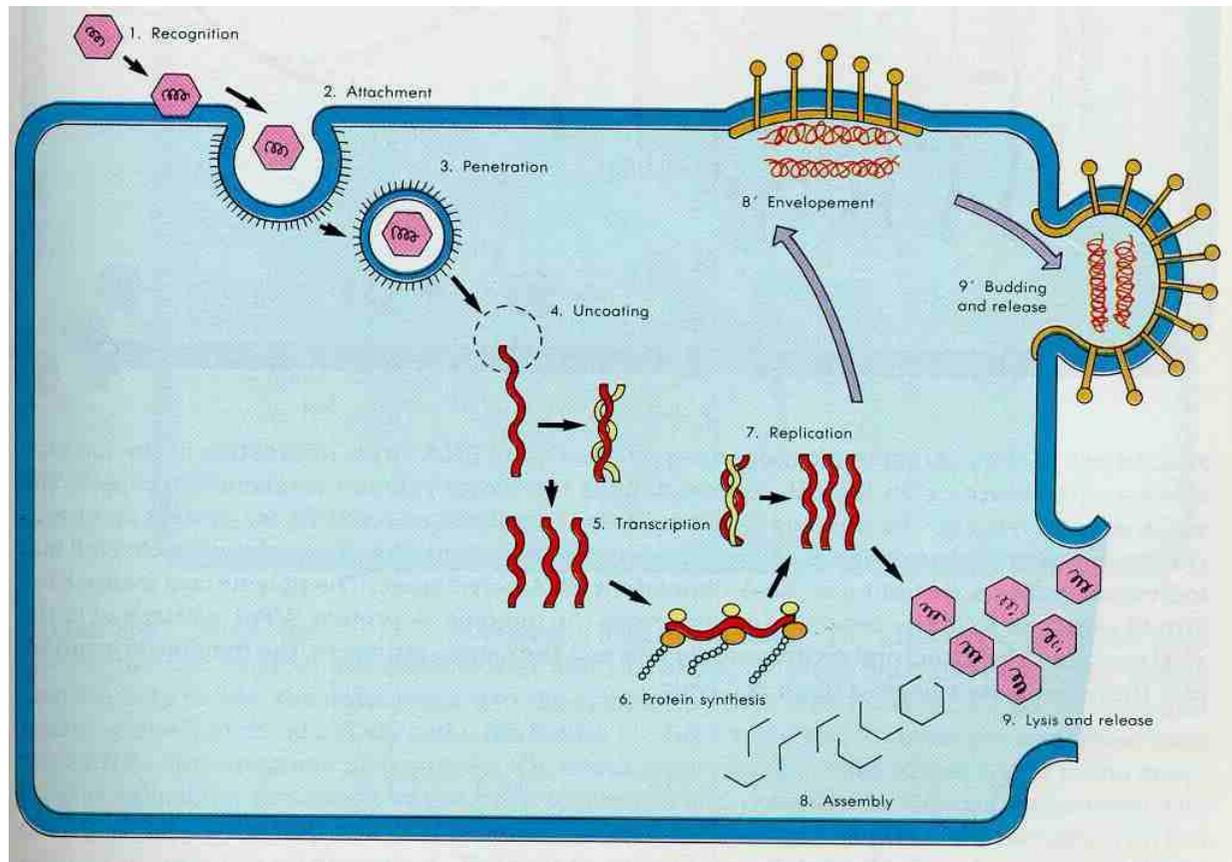
Programa Municipal de Hepatites Virais – São Paulo/SP

O vírus da Hepatite C



REPRESENTAÇÃO ESQUEMÁTICA DO GENOMA DO HCV

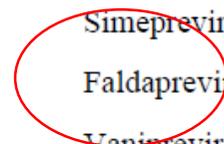
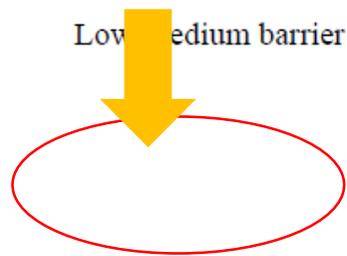




Year	Natural history, virology and model systems	DAA development	HTA development	Clinical advances
1975	Description of non-A, non-B hepatitis			
1978	Transmission to chimpanzees	Model for <i>in vivo</i> efficacy of DAAs and HTAs		
1986				Type I IFN for treatment of non-A, non-B hepatitis
1989	Identification of HCV			
1992				Blood supply screening implemented
1993	Genome organization, polyprotein processing, viral enzyme motifs	HCV genotype diversity		Genotype-specific responses to therapy
1995	Cell-free assays for the NS3-NS4A protease	High-throughput screening for protease inhibitors		
1996	High-resolution structure of the NS3-NS4A serine protease	Structure-assisted protease inhibitor design		
	Cell-free assays for the NS5B RNA-dependent RNA polymerase	High-throughput screening for polymerase inhibitors		
1997	RNA transcripts from consensus cDNA clones are infectious in chimpanzees	Validated functional cDNA for development of biochemical and cell-based screening assays		
1998	E2 binds CD81, the first candidate HCV receptor identified	Development of a surrogate assay for potential virus-neutralizing antibodies	Screens for receptor-blocking antibodies	Ribavirin, combined with IFN- α , enhances SVR
1999	The RNA replicon system	Inhibitor efficacy in cell-based assays; unbiased cell-based screens for RNA replication inhibitors	Identification of host factors required for HCV RNA replication (siRNA, proteomics)	
	High-resolution structure of the NS5B RNA-dependent RNA polymerase	Structure-assisted polymerase inhibitor design		

- Passado: tínhamos drogas cujo mecanismo de ação estava fora do mecanismo de ação viral. Ex: Interferon, Ribavirina.
- Presente: temos drogas ação direta no vírus e com isto risco **RESISTÊNCIA!**

Inhibitor class	Resistance	Potency	Lead compounds ^a
DAAs			
NS3-NS4A protease inhibitors			
First generation	Low to medium barrier	High toward genotype 1, lower toward genotypes 2 and 3	Telaprevir (Incivek, Incivo) Boceprevir (Victrelis) Simeprevir (TMC-435) Faldaprevir (BI201335) Vaniprevir (MK-7009) Asunaprevir (BMS-650032) ABT-450 Danoprevir (RG7227) Sovaprevir (ACH-1625) Vedroprevir (GS-9451)
Second generation	Medium barrier	High; expected to be pan-genotypic	MK-5172 Neceprevir (ACH-2684)



NS5A inhibitors ^b		Low-medium barrier	Very high	
		↑		Daclatasvir (BMS-790052)
		↓		Ledipasvir (GS-5885)
		↓		ABT-267
		↓		GSK2336805
		↓		ACH-3102
		↓		IDX-719
		↓		MK-8742
		↓		PPI-668
		↓		GS-5816
<hr/>				
NS5B polymerase inhibitors				
Nucleoside/nucleotide analogs	Medium-high barrier	High; pan-genotypic		Sofosbuvir (GS-7977)
				Mericitabine (RG7128)
				VX-135
Non-nucleoside analogs ^c	Low barrier, escape mutants have high fitness	Medium-high; highly genotype or subtype specific		ABT-333 (Palm-I/C)
				BI207127 (Thumb-I/A)
				BMS-791325 (Thumb-I/A)
				Lomibuvir (VX-222) (Thumb-II/B)
				ABT-072 (Palm-I/C)
				Setrobuvir (RG7790) (Palm-I/C)
				GS-9669 (Thumb-II/B)
				TMC647055 (Thumb-I/A)

Como evitar a Resistência

- Uso adequado, medicamento certo e paciente certo;
- Seguir PCDT;
- Monitorar o paciente.

MINISTÉRIO DA SAÚDE

PROTOCOLO CLÍNICO E
DIRETRIZES TERAPÊUTICAS PARA
**HEPATITE C
E COINFECCÕES**

BRASILIA
2015

Esquema terapêutico relacionado a cada genótipo do HCV

Genótipo	Perfil da infecção		
Genótipo 1	Monoinfecção HCV	Sofosbuvir + simeprevir	12 semanas
	Monoinfecção HCV	Sofosbuvir + daclatasvir	12 semanas
	Cirrose Child-Pugh B e C, paciente experimentado com BOC/TEL ou coinfeção HIV/HCV	Sofosbuvir + daclatasvir	24 semanas
Genótipo 2	Não há distinção entre perfis*	Sofosbuvir + ribavirina	12 semanas
Genótipo 3	PR autorizado	Sofosbuvir + PR	12 semanas
	PR contraindicado	Sofosbuvir + Daclatasvir	12 semanas
Genótipo 4	PR autorizado	Daclatasvir + PEG-IFN + ribavirina	24 semanas
	PR contraindicado	Sofosbuvir + daclatasvir	12 semanas