MEDICINA
USP 100 ANOS 1912 - 2012

Mecanismo de ação dos medicamentos utilizados para o tratamento de Hepatite B.

Prof. Dra. Suzane Kioko Ono
Disciplina de Gastroenterologia Clínica
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Reunião Clínica do Programa Municipal de Hepatites Virais
CCD/COVISA /SMS São Paulo
"Hepatite B - Novo Protocolo de Tratamento
e Tratamento da Gestante"
São Paulo, 09 de novembro de 2016.

Conflitos de interesse

PI ou subinvestigador Clinical trials
Phase III clinical trials – Drug: Entecavir – Chronic hepatitis B (BMS)
Phase III clinical trial – Drug: Telbivudine – Chronic hepatitis B (Novartis)
Phase III – Drug BIP48 – HCV (Fiocruz)
Phase III – Clinical trials – Drug Sorafenib – HCC (Bayer)

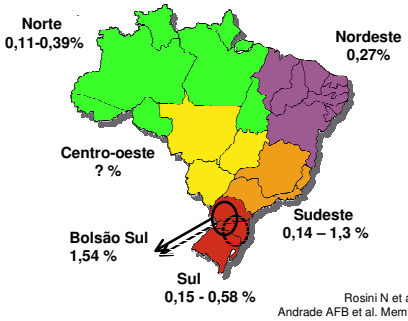
Patrocínios de eventos –
USP/Universitat Barcelona (MSD, Roche, BMS, Glaxo, Gilead)

Auxílios pesquisas de órgãos de fomento
FAPESP e CNPq

Alves de Queiroz Family fund for research

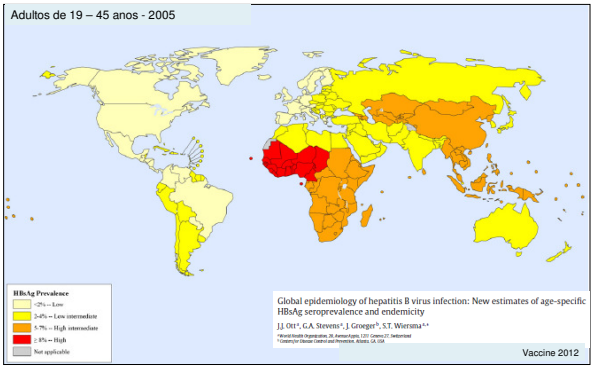
Século XXI

Prevalência do **AgHBs** no Brasil (doadores de sangue)



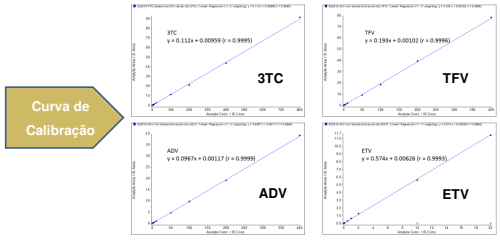
Rosini N et al. Braz J Infect Dis 2003
Andrade AFB et al. Mem Inst Oswaldo Cruz 2006
Salles NA et al. Rev PANAM Salud Publica 2003
Nascimento MC et al. J Med Virol 2008
Valente VB et al. Ver Soc Bras Med Tropical 2005

Prevalência estimada da hepatite crônica B



FARMACOCINÉTICA

- **Dosagem plasmática do antiviral: confirmar não adesão**
- **1ª avaliação de adesão**
  - **Grupo com HBV-DNA +**
- **Cromatografia Líquida (HPLC) – Espectrometria de Massas (MS)**



Faixa linear para os quatro analitos:
3TC 1 – 800 ng/mL; TFV 0.05 – 400 ng/mL; ADV 0.25 – 400 ng/mL; ETV 0.01 – 20 ng/mL.

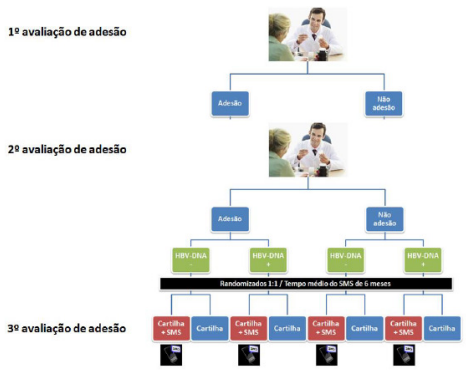


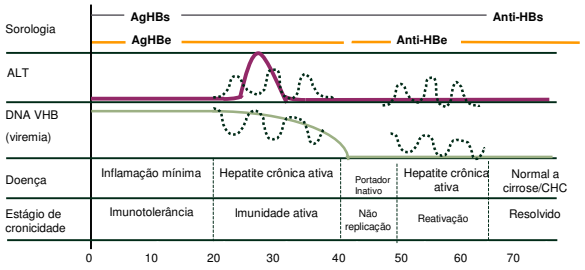
Figura 10. Representação esquemática do desenho do estudo

RESPOSTA VIROLÓGICA DE ACORDO COM A AVALIAÇÃO DE ADESÃO, DIVIDIDOS POR REGIME DE TRATAMENTO

Tratamento	Adesão			Não adesão		
	HBV-DNA Neg n (%)	HBV-DNA Pos n (%)	Total	HBV DNA Neg n (%)	HBV DNA Pos n (%)	Total
3TC, n = 98 ADV, n = 6 TDF, n = 20 ETV, n = 12 3TC + ADV, n = 28 3TC + TDF, n = 19 Total, n = 183	56,8 % (104)			43,2% (79)		

Pacientes com não adesão tem maior frequência de HBV-DNA.

História Natural da Hepatite B crônica



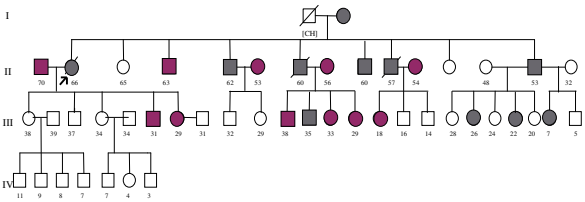
Risco de cronicidade de acordo com a idade de infecção:

Neonato > 90%
12 anos < 10%

Genotype/ subgenotype	Number of patients	Age (years) at HBeAg clearance: 50th percentile	Age (years) at HBeAg clearance: 75th percentile
A2	34	19.4	32.1
B6	6	19.5	27.5
C2	36	47.8	58.1
D	305	18.0	27.3
F1	126	16.1	24.5

McMahon BJ Hepatol Int 2009

Família ocidental 20



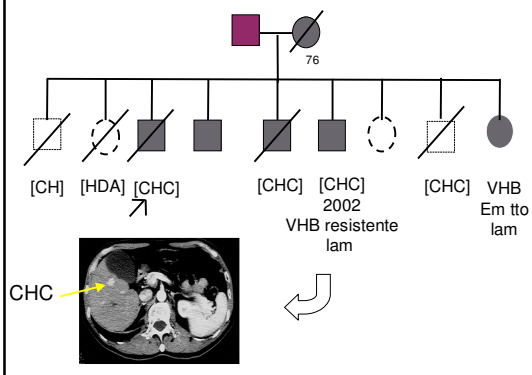
Sexo feminino AgHBs positivo

Sexo masculino Anti-HBs positivo

Indivíduo falecido

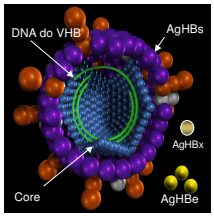
Ono-Nita et al. BMC Family practice 2004

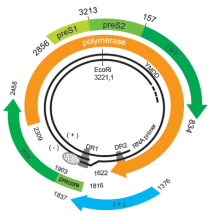
Família oriental 14



CHC

Carrilho FJ, Ono-Nita et al. Brazilian J Med and Biol Res 2005





Kao J-H. Korean J Intern Med 2011

Organização do Genoma do VHB

- Família *Hepadnaviridae*
- Tropismo por hepatócitos
- Replicação dependente da transcriptase reversa
- Partícula icosaédrica e envelopada
- Proteínas
  - Envelope (AgHBs, MHBs e LHBs)
  - Core (AgHBc) e AgHBe
  - Polimerase
  - Proteína X

Replicação do VHB

DNA Fita dupla

↓ transcrição

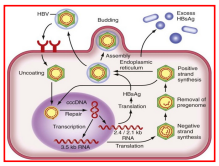
RNA pregenômico

Inibidor Transcriptase Reversa ⊣ Transcrição reversa

DNA fita simples (fita negativa)

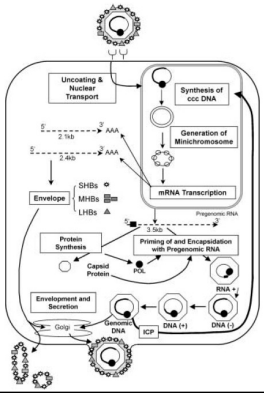
↓ Síntese fita positiva DNA

DNA fita dupla



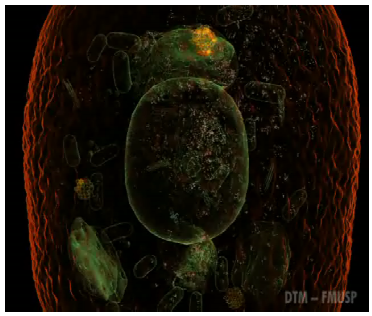
Perillo R in: Sleisenger & Fordtran's, 9th Ed - 2010
Doo & Ghany, Clin Liver Dis - 2010

Ciclo de vida e replicação do HBV



- Ligação e entrada;
- Remoção do envelope e transporte nuclear;
- Reparo do genoma;
- Transcrição e tradução;
- Formação do nucleocapsídeo;
- Síntese do DNA viral;
- Secreção de vírions e partículas não infecciosas.

Locarnini, Sem. Liv. Dis., 2003



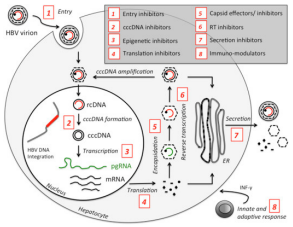


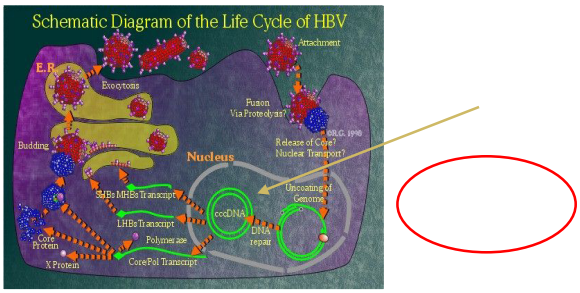
Fig. 1. Schematic representation of the inhibitors of Hepatitis B virus replication cycle. cccDNA, covalently closed circular DNA; ER, endoplasmic reticulum; HBV, hepatitis B virus; INF, interferon; mRNA, messenger RNA; pgRNA, pregenomic RNA; rcDNA, relaxed ci...

Sebastien Boucle, Leda Bassit, Maryam Ehteshami, Raymond F. Schinazi

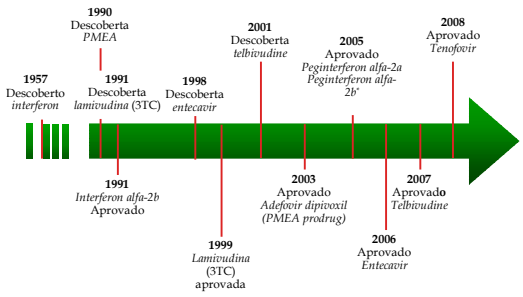
Toward Elimination of Hepatitis B Virus Using Novel Drugs, Approaches, and Combined Modalities

Clinics in Liver Disease, Volume 20, Issue 4, 2016, 737–749

http://dx.doi.org/10.1016/j.cld.2016.07.001



Avanços no tratamento da hepatite B



Modificado de ClinicalCareOptions.com

Table 1
Advantages and disadvantages of IFN versus NUC therapies for chronic hepatitis B

	IFN	NUCs	Advantage
Duration of treatment	Finite (approx. 12 mo)	Indefinite	IFN
Antiviral resistance	None	LMV > TBV > ADV > ETV/ TDF	IFN
HBeAg and HBsAg loss	Modest, Genotype Dependent	Rare	IFN
Route of administration	Injection	Oral	NUC
Antiviral activity	Modest	Potent: ETV/TDF/ TBV > LMV > ADV	NUC
Side effects	Common, Potentially Severe	Negligible	NUC
Safety in pregnancy	Pregnancy class C	Pregnancy class B: TBV and TDF Safety data in humans: LMV, TBV and TDF	NUC
Safety in decompensated cirrhosis or liver failure	No	Yes	NUC

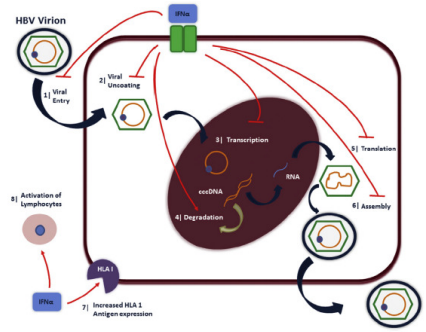


Fig. 1. Mechanism of action of interferon (IFN) therapy for chronic hepatitis B virus (HBV) infection. HBV lifecycle and mechanisms of action of IFN therapy in chronic hepatitis B. Potential effects of IFN include blocking (1) virus entry, (2) uncoating of virion, (3) transcription of viral DNA into RNA, (4) degradation of ccc DNA, (5) translation of viral RNA into proteins, (6) assembly of nucleocapsids, (7) increase HLA1 antigen expression, and (8) activation of CD8 T cells.

Konerman Clin liv Dis 2016

Journal of Viral Hepatitis, 2015 doi:10.1111/jvh.12418

REVIEW

Pegylated interferon alfa for chronic hepatitis B: systematic review and meta-analysis

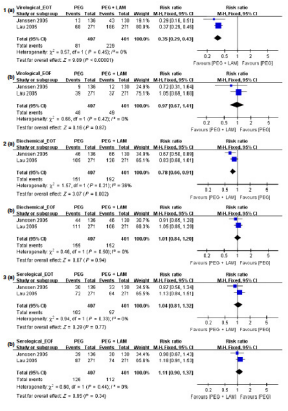
V. Kim, R. M. Abreu, D. M. Nakagawa, R. M. Baldassare, F. J. Carrilho and S. K. Ono *Division of Clinical Gastroenterology and Hepatology, Department of Gastroenterology, University of São Paulo School of Medicine, São Paulo, Brazil*

Received November 2014; accepted for publication March 2015

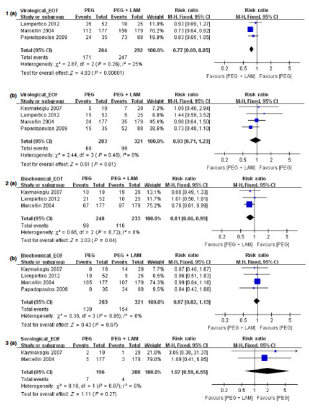
SUMMARY. Conventional interferon alfa and nucleos(t)ide analogues, such as lamivudine, are frequently used for chronic hepatitis B (CHB) treatment, but are associated with adverse effects and viral resistance. Here we performed a systematic review and meta-analysis evaluating all studies of pegylated interferon alfa (PEG-IFNα) treatment in hepatitis B e antigen (HBeAg)-positive and HBeAg-negative patients with CHB. We searched electronic databases – PubMed, EMBASE, Cochrane Library and LILACS – for randomized controlled trials evaluating PEG-IFNα therapy between 1999 and September 2014. Virological response was the primary outcome. We identified 14 studies involving 2829 patients. Our analysis revealed that PEG-IFNα + lamivudine combination therapy produced better virological and biochemical responses than PEG-IFNα monotherapy in HBeAg-positive and HBeAg-negative patients at the end of treatment. PEG-IFNα + adefovir dipivoxil achieved better seroconversion rate than PEG-IFNα in HBeAg-positive patients at the end of treatment. The present findings demonstrated a beneficial response rate following PEG-IFNα combination therapy with nucelos(t)ides among HBeAg-positive and HBeAg-negative patients with CHB. Further trials are needed to investigate simultaneous and sequential therapy strategies.

Keywords: chronic hepatitis B, meta-analysis, pegylated interferon alfa, randomized controlled trials.

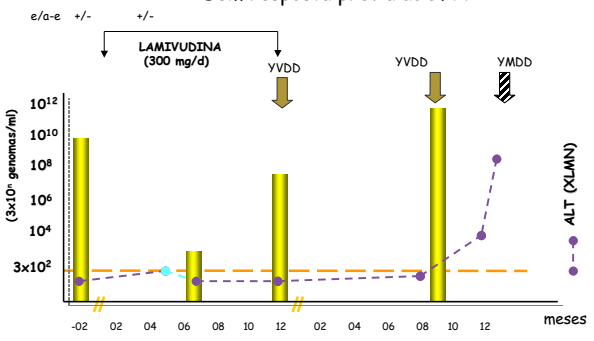
AgHBe +



AgHBe -



JB, masc., 44a, com HC por VHB
Sem resposta prévia ao IFN



Modificado de Da Silva LC.

REVIEWS

Antiviral Drug-Resistant HBV: Standardization of Nomenclature and Assays and Recommendations for Management

Anna S. Lok,[1] Fabien Zoulim,[2] Stephen Locarnini,[3] Angeline Bartholomeusz,[3] Marc G. Ghany,[4] Jean-Michel Pawlotsky,[5] Yun-Fan Liaw,[6] Masashi Mizokami,[7] and Carla Kuiken,[8] and the Hepatitis B Virus Drug Resistance Working Group

Substantial advances have been made in the treatment of chronic hepatitis B in the past decade. Approved treatments for chronic hepatitis B include 2 formulations of interferon and 4 nucleos(t)ide analogues (NAs). Sustained viral suppression is rarely achieved after withdrawal of a 48-week course of NA therapy, necessitating long, and in many cases, indefinite treatment with increasing risk of development of drug resistance. Antiviral resistance and poor adherence are the most important factors in treatment failure of hepatitis B. Thus, there is a need to standardize nomenclature relating to hepatitis B antiviral resistance, and to define genotypic, phenotypic, and clinical resistance to NA therapy. (HEPATOLOGY 2007;46:254-265.)

Resistência antiviral e **baixa aderência ao tratamento**

Fatores mais importantes na **falha ao tratamento** da Hepatite B

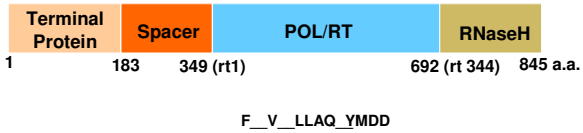
Definições Resistência

- Genotípica – mutações no genoma do VHB selecionadas durante tto.
- Virológica – aumento da viremia durante o tramento
- Clínica – aumento da ALT, piora da função hepática e/ou histológica
- Fenotípica – diminuição da susceptibilidade *in vitro* ao antiviral
- Cruzada – antiviral seleciona variante resistente a outro antiviral

Obs: Recorrência – reaparecimento da viremia após interrupção do tratamento

Re-take over – retorno do VHB selvagem após interrupção do antiviral

Mutações de resistência primária

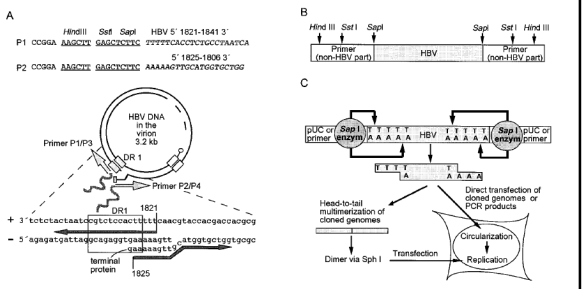


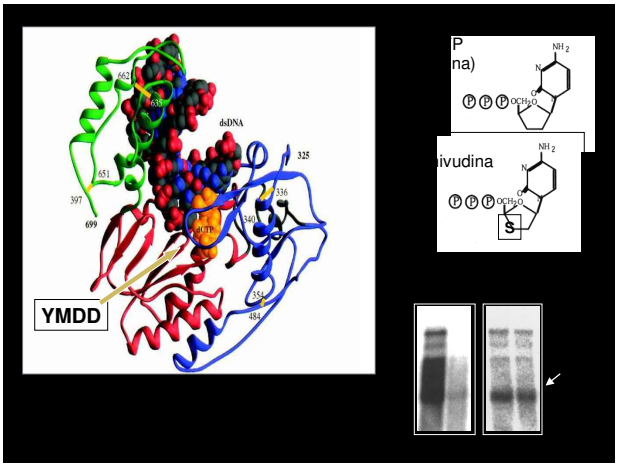
F__V__LLAQ_YMDD

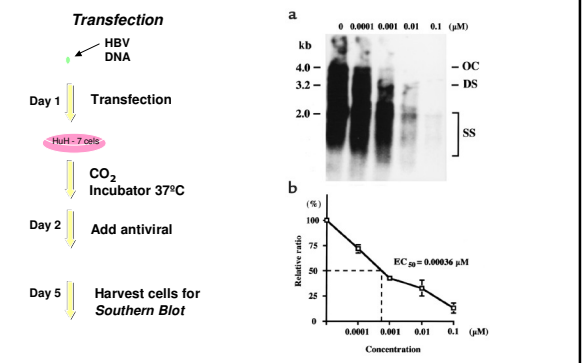
I(G)	II(F)	A	B	C	D	E
LMV Resistance			rtA181T/V (rtL180M)	rtM204V/I	rtQ215S	
L-dT Resistance				rtM204I		
ADV Resistance		rtV84M	rtA181T/V	rtV214A rtQ215S rtN236T		
TDF Resistance*			rtA194T/rtV214A/rtQ215S			
ETV Resistance*			rtS184G	rtS202I		rtM250V

* Em associação á resistência á lamivudina

Locarnini S
www.vidrl.org.au/publications/hep_updates.htm





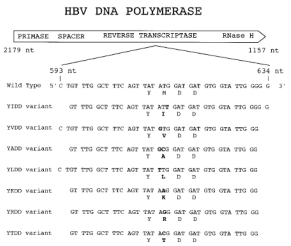


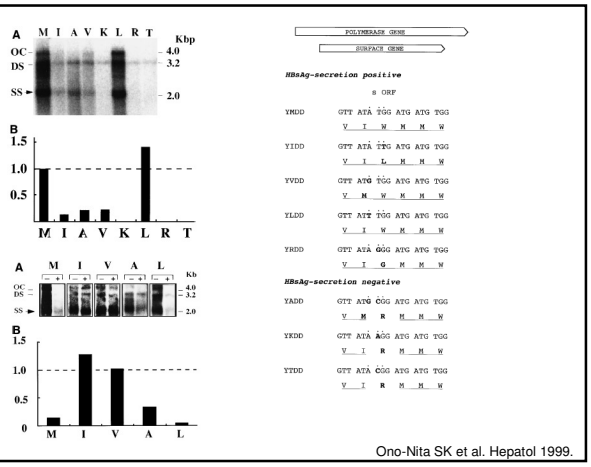
Ono-Nita SK et al. Hepatology 1999.
Ono SK et al. J Clin Invest 2001.

YMDD Motif in Hepatitis B Virus DNA Polymerase Influences on Replication and Lamivudine Resistance: A Study by *In Vitro* Full-Length Viral DNA Transfection

Suzane Kioko Ono-Nita,[1] Naoya Kato,[1] Yasushi Shiratori,[1] Tsutomu Masaki,[1] Keng-Hsin Lan,[1] Flair José Carrilho,[2] and Masao Omata[1]

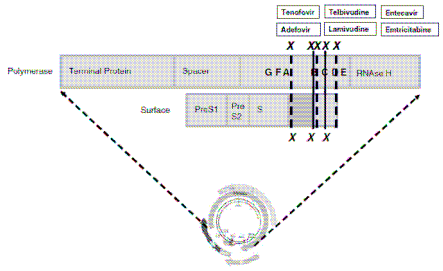
Hepatology 1999;29:939-945





Ono-Nita SK et al. Hepatol 1999.

Sobreposição das fases de leitura aberta da polimerase e gene de superfície



The polymerase L528M mutation cooperates with nucleotide binding-site mutations, increasing hepatitis B virus replication and drug resistance

Suzane Kioko Ono,[1,2] Naoya Kato,[1] Yasushi Shiratori,[1] Jun Kato,[1] Tadashi Goto,[1] Raymond F. Schinazi,[3] Flair José Carrilho,[2] and Masao Omata[1]

J. Clin. Invest. **107**:449–455 (2001).

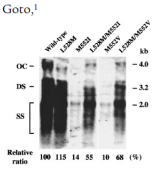
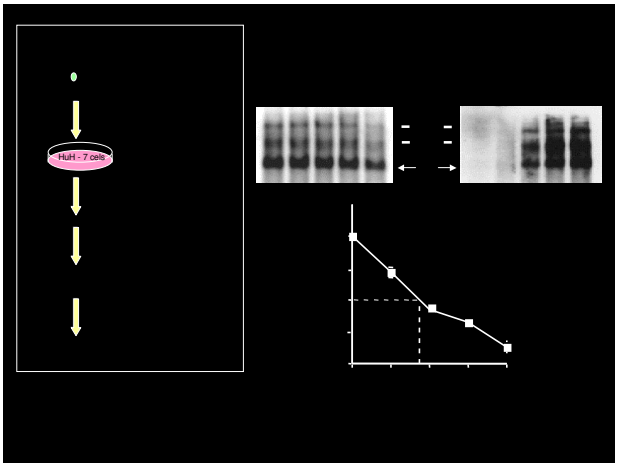


Table 1
EC_{50} values of compounds and level of replication of wild-type and five mutants HBV at 10 μM concentration treatment

	Wild		L528M		M552I		M552V		L528M/M552I		L528M/M552V	
Compound	10 μM[A]	EC_{50}	10 μM[A]	EC_{50}	10 μM[A]	EC_{50}	10 μM[A]	EC_{50}	10 μM[A]	EC_{50}	10 μM[A]	EC_{50}
Lamivudine	1.3 ± 0.2	0.56	59.2 ± 8.6	>10	176.8 ± 17.9	>80[B]	76.9 ± 15.8	33[B]	111.7 ± 17.3	>10	126.7 ± 9.6	>80[B]
Adefovir	10.5 ± 6.1	0.58	8.8 ± 10.3	0.45	30.8 ± 20.0	4.5[B]	32.5 ± 2.9	4.9[B]	47.2 ± 6.5	9.5	23.8 ± 13.3	2.2[B]
Entecavir	3.6 ± 0.4	0.0004	12.7 ± 4.9	0.0005	16.4 ± 3.5	0.06	5.2 ± 1.0	0.003	42.3 ± 5.3	0.25	34.7 ± 18.1	0.28
(+)-BCH-189	103.2 ± 22.3	>10	142.2 ± 28.0	>10	107.5 ± 15.6	>10	131.0 ± 10.9	>10	98.3 ± 8.9	>10	173.8 ± 15.4	>10
(+)-FTC	13.6 ± 12.8	1.85	39.6 ± 6.4	5.1	98.7 ± 20.2	>10	83.5 ± 10.6	>10	125.1 ± 30.8	>10	122.3 ± 4.7	>10
(−)-FTC	7.1 ± 1.0	0.24	31.5 ± 5.5	2.7	105.9 ± 32.2	>10	102.3 ± 25.1	>10	144.1 ± 19.0	>10	87.6 ± 12.1	>10
(+)-FTC	79.7 ± 5.4	>10	111.0 ± 12.3	>10	104.8 ± 4.5	>10	108.3 ± 23	>10	96.6 ± 12.4	>10	101.9 ± 8.9	>10
L-D4FC	1.5 ± 0.2	0.033	4.8 ± 6.7	0.13	145.5 ± 31.6	>10	5.4 ± 6.5	1.8	99.5 ± 9.9	>10	128.3 ± 28	>10
L-FMAU	16.5 ± 10.0	0.053	39.6 ± 17.8	1.2	91.8 ± 13.8	>10	9.6 ± 15.9	0.74	127.3 ± 20	>10	104 ± 24.4	>10
D-DAPD	75.9 ± 23.6	>10	99.4 ± 8.9	>10	132 ± 29.9	>10	118.7 ± 29.6	>10	134.6 ± 4.1	>10	105.7 ± 9.3	>10
(−)-Carbovir	57 ± 32.2	>10	74.9 ± 6.6	>10	95.7 ± 30.3	>10	107.8 ± 19.7	>10	92.4 ± 8.7	>10	95.7 ± 30.3	>10

[A]Numbers indicate the mean ± SD in percent of replication of wild-type and mutant HBV treated with 10 μM of compounds. [B]Ref. 25.



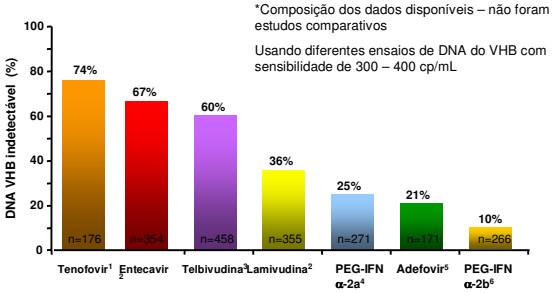
L-FMAU	0,053	1,2	>10,0	0,74	>10,0	>10,0
MCC-478	0,027		2,6	3,3		2
Adefovir	0,58	0,45	4,5	4,9	9,5	2,2
Entecavir	0,00036	0,00054	0,06	0,0031	0,25	0,28

Hepatitis B drugs

Drug	Company	Phase	EC50% μM
Lamivudine	Glaxo	IV	0.56*
Adefovir	Roche - Schering Plough	IV	0.58*
Peg-IFN a2a	Roche	IV	
Entecavir	BMS	IV	0.00036*
Tenofovir	Gilead Sciences	IV	0.1**
Ldt (Telbivudine)	Indenix Pharmaceuticals	IV	
Emtricitabine(Coviracil)	Gilead Sciences	III	0.24*
Val-LdC	Indenix Pharmaceuticals	II	
Clevudine (L-FMAU)	Pharmasset	III Halt 2009	0.053*

*Ono-Nita SK, JCI, 2001.
**Lada O, Antiviral Ther 2004

DNA do VHB indetectável Pacientes AgHBe positivos *

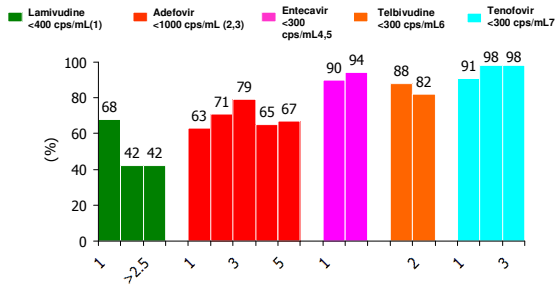


*Composição dos dados disponíveis – não foram estudos comparativos

Usando diferentes ensaios de DNA do VHB com sensibilidade de 300 – 400 cp/mL

[1]Heathcote, AASLD 2007; [2]Chang, NEJM 2006; [3]Lai CL AASLD 2005; [4]Lau, NEJM 2005; [5]Marcellin, NEJM 2003 [6]Janssen, Lancet 2005

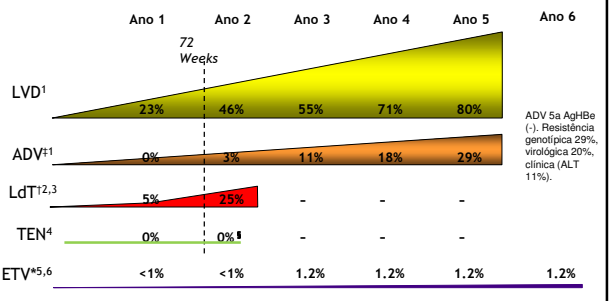
Comparação dos antivirais para pacientes AgHBe (-)
Porcentagem de DNA do VHB indetectável*



*Composição dos dados disponíveis – não foram estudos comparativos

1. Hadziyannis S, *et al. Hepatology* 2000;32:847–851. 2. Hadziyannis S, *et al. NEJM 2005; 352: 2673–2681*. 3. Hadziyannis S, *et al. Hepatology* 2005; 42 (suppl 1):754A (Abstract LB14). 4. Lai C-L et al. NEJM 2006;354: 1011–1020; 5. Shouval D, et al. *EASL* 2006, Vienna, Austria, Oral abstract 45 6. Lai CL, AASLD 2006

Incidência cumulativa resistência antiviral

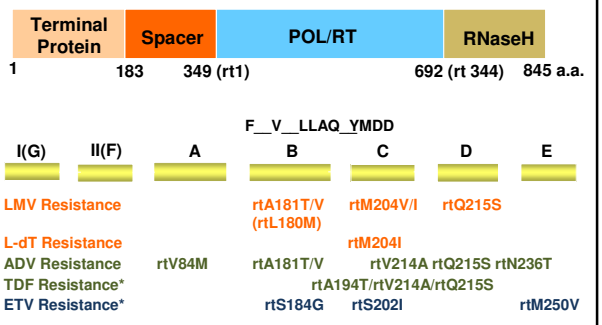


ADV 5a AgHBe (-). Resistência genotípica 29%, virológica 20%, clínica (ALT 11%).

Estudos com populações, critérios de exclusões, seguimentos e desfechos diferentes* ; † Virgens AgHBe (+) ; ‡ Virgens AgHBe (-); N/A not available

1. Locarnini S. *Hepatol Int*. 2008;2:147-51. 2. Lai CL, et al. *N Engl J Med*, 2007;357:2576-8; 3. Liaw YF, et al. *Gastroenterology* 2009;136:486-95. 4. Snow-Lampart A, et al. AASLD Oct 31-Nov 4, 2008, San Francisco, USA. Oral Presentation 977 *Hepatology* 2008;48:745A. 5. Baraclude EU SmPC, February 2009. 6. Tenney et al. EASL April 22-26, 2009, Copenhagen, Denmark, Oral Presentation 176; 7Hadziyanis et al. Gastroenterol 2006.

Primary resistance mutations



* In association to lamivudine resistance

Locarnini S
www.vidrl.org.au/publications/hep_updates.htm

Mutações de resistência Primária
Codons importantes

B-domain	169	C-domain	202
	180		204
	181		
	184		
D-domain	236	E-domain	250

TOTAL 8

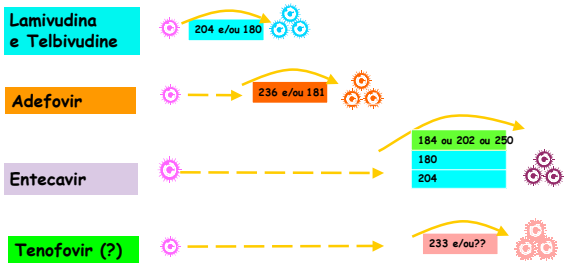
169 180 181 184 202 204 236 250

Proposed Key Pathways:

- rtM204V/I → L-NUCLEOSIDES (LMV, LdT) ETV in LMV-Experienced
- rtN236T → ACYCLIC PHOSPHONATES (ADV, TDF)
- rtA181T/V → SHARED
- rtL180M+rtM204V+T184 or S202 or M250 → ETV (naïve)
- rtA181T+rtI233V+rtN236T+rtM250L → MDR

Barreira Genética

Número necessário de mutações no VHB para diminuir eficácia do medicamento



US prescribing information for Epivir-HBV®, Hepsera® and Baraclude™
Fung SK, *et al. J Hepatol* 2006; **44**:283–290
Locarnini S, *et al. J Hepatol* 2006; **44**:422–431
Tenney DJ, *et al. Antimicrob Agents Chemother* 2004; **48**:3498–3507
Schildgen O et al. J Clin Microbiol 2010; **48**: 631-4.

Table 2. *In vitro* and *in vivo* Significance of Antiviral-Resistant Mutations

	Lamivudine	Clevudine	Telbivudine	Entecavir	Adefovir	Tenofovir
HBV	·Fold Resistance	·Fold Resistance	·Fold Resistance	·Fold Resistance	·Fold Resistance	·Fold Resistance
Wild-type	1	1	1	1	1	1
M204I	>100 [a, h]	>100 [a]	4 [d]	1 [d]	<1-8 [a, h, c]	<1 [g]
L180M + M204V	>100 [a, h]	>100 [a]	NA	5-6 [e, f]	<1-4 [a, h, c]	3-6 [f, g]
A181 T/V	1-2 [d, h]	NA	5-6 [d]	1-4 [d]	1-3 [d]	1 [d]
N236T	1 [f, h]	NA	3 [d]	<1 [f]	3 [f]	5 [f]
I169T + V173L + M250V	>1000 [d, h]	NA	>1000 [d]	>700 [e]	1 [d]	<1 [g]
T184G + S202I *	>1000 [d, h]	NA	35 [d]	>700 [e]	2 [d]	6 [d]
A194T	NA	NA	NA	NA	NA	2 [h]

* (+ L180M + M204I/V); NA = Not Available
2 - 9 fold → no or low level of resistance; 10 - 99 fold → medium level of resistance; >100 fold → high level of resistance
References: [a] Chin et al.[53]; [b] Delaney et al. (2001)[34]; [c] Ono et al.[73]; [d] Sozzi et al.[74]; [e] Tenney et al.[47]; [f] Brunelle et al.[48]; [g] Sheldon et al.[36]; [h] Delaney et al. (2006).[50]

Lok et al. Hepatology 2007

Fatores associados com a emergência de virus resistentes

- Potência Antiviral
- Nível de exposição à droga
- Estrutura química
- Número de mutações necessárias para resistência (barreira genética)

Droga Antiviral

Vírus

Paciente

- Velocidade de Replicação
- Fidelidade de Replicação
- Mutações prré-existentes
- Replicação fitness
- Replicação espaço
- AgHBe (+) vs AgHBe (-)

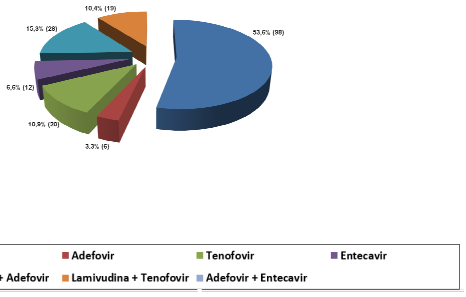
- Tratamento prévio
- Aderência
- Estado de imunidade
- Persistência de mutações no cccDNA
- Metabolismo
- Massa corpórea

Locarnini S, et al. Antivir Ther 2004;9:679–693. Locarnini S, et al. Antivir Ther 2007;12:H15–H23. Ghany M & Liang TJ. Gastroenterology 2007;132:1574–1585. Zoulim F, et al. Antiviral Res 2004;64:1–15. Locarnini S, et al. J Hepatol 2003;39:S124–S132.

Estratégia para evitar ou detectar precocemente a resistência

- Monitorar a carga viral do DNA do VHB a cada 3 a 6 meses.
- 1ª linha - antiviral com a maior potência e com rápida capacidade de supressão viral (desenvolvimento de resistência depende da replicação viral)
- Importância da aderência ao tratamento

Shaw T & cols. HBV drug resistance: Mechanisms, detection and interpration. Journal of Heptaology, 2006



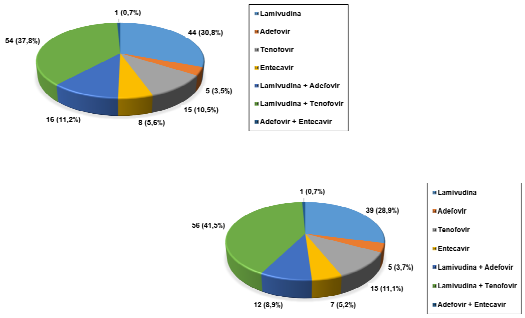
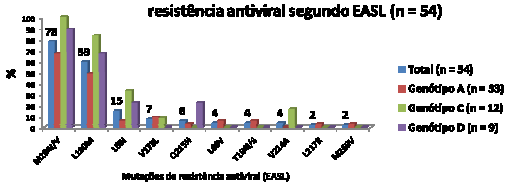


Tabela 12. Frequência de mutações de resistência antiviral de acordo com o esquema terapêutico. HCFMUSP, dezembro de 2010 a agosto de 2011 (n = 183)

Tratamento antiviral	Número de pacientes	Mutantes - n (%)
Lamivudina	98	25 (25,5)
Adefovir	6	0 (0,0)
Tenofovir	20	1 (5,0)
Entecavir	12	0 (0,0)
Lamivudina + Adefovir	28	11 (39,3)
Lamivudina + Tenofovir	19	6 (31,6)
Total	183	43 (23,5)

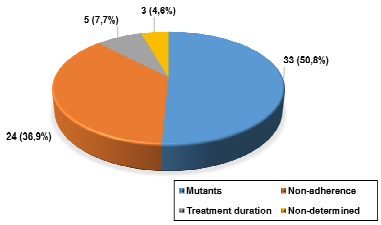
Frequência total e por genótipos das mutações de resistência antiviral segundo EASL (n = 54)



Mutações de interesse baseado no EASL v2012 (DeepChek®- HBV/HDV software v1.4).

CARTILHA DE ORIENTAÇÃO AO TRATAMENTO

Principais fatores envolvidos na falha ao tratamento



- Alta taxa de não adesão na 1ª avaliação (43%).
- As principais causas de falha do tratamento são mutações de resistência as drogas (51%) e não-adesão aos antivirais (37%).
- Conhecimento sobre o perfil de resistência antiviral e status de adesão possibilita a troca do antiviral e a implementação de estratégias para melhorar a adesão, respectivamente.